Antimicrobial Resistance Benchmark 2021

access to medicine FOUNDATION

ACKNOWLEDGEMENTS

The Access to Medicine Foundation would like to thank the following people and organisations for their contributions to this report.[1]

FUNDERS

UK Foreign, Commonwealth and Development Office
The Dutch Ministry of Health, Welfare and Sport
AXA Investment Managers
Wellcome Trust

ACCESS TO MEDICINE FOUNDATION

The Access to Medicine Foundation is an independent non-profit organisation based in the Netherlands. It aims to advance access to medicine in low- and middle-income countries by stimulating and guiding the pharmaceutical industry to play a greater role in improving access to medicine.

Address
Naritaweg 227-A
1043 CB, Amsterdam
The Netherlands

Contact
For more information about this publication, please contact
Fatema Rafiqi, Research Programme Manager
frafiqi@accesstomedicinefoundation.org
+31 (0) 20 215 35 35
www.amrbenchmark.org

1 This acknowledgement is not intended to imply that the individuals and institutions referred to above endorse the Antimicrobial Resistance Benchmark methodology, analyses or results. Decisions regarding the final analysis were ultimately made by the Access to Medicine Foundation.

About the cover: On the cover is a young boy from Tanzania, a country where resistant bacteria is widespread as are many issues related to access and stewardship.

Photo: Jasmin Merdan (Getty Images)

Progress against drug resistance must accelerate

For the last five years, we have been tracking how the biggest pharmaceutical companies in the antibiotic market have tackled the rise of antimicrobial resistance (AMR) and the global need for appropriate access to antimicrobials. This third Antimicrobial Resistance Benchmark has identified progress in some areas, including a significant increase in forward planning to make new medicines available in low- and middle-income countries.

That is the good news. The bad is news that there is still a widespread failure to get established antibiotics to patients in resource-poor settings, where the risk of drug-resistant infections is greatest. Just one third of the products we examined had any kind of strategy in place to address access – such as price adjustments to make medicines more affordable, or licensing agreements to boost supply. This lack of appropriate access forces doctors to use suboptimal treatments, giving pathogens further opportunities to develop resistance and thereby stoking the rise of resistance.

When it comes to R&D, Big Pharma's engagement appears to have stabilised after years of retrenchment – yet the pipeline of new products remains thin, and progress is heavily reliant on a few large companies, as well as the many small biotechnology firms with precarious finances. Generic medicine manufacturers are making further advances in stewardship, including several large Indian players that have stayed focused on AMR despite the ravages of COVID-19 in their home country.

What is needed now is a greater sense of urgency from all players. We must learn the lessons from the coronavirus pandemic. The unacceptable inequity in global access to COVID-19 vaccines must not be repeated when it comes to defending all communities against superbugs.

Antimicrobial resistance is not a problem for the future. It is here already, with an estimated 750,000 people dying each year from drug-resistant infections. At the same time, 5.7 million people also die annually from treatable infections because they lack access to medicines. The combination of more superbugs and inadequate treatment is brewing up a lethal cocktail that threatens to unleash spiralling levels of drug resistance, driven by natural selection.

We know what needs to be done to counter this threat. There are tried-and-tested tools that can increase local availability of vital antibiotics in poorer nations, such as wider product registration, technology transfers and strong, long-lasting partnerships. All these things have been shown to improve access by pooling the resources across a fragile healthcare ecosystem.

Back in January 2016, more than 100 companies and trade organisations came together to sign the Davos Declaration, committing to developing better ways to provide dependable and sustainable supplies of antibiotics, and urging governments to work with them. Since then, there have clearly been moves in the right direction. Companies and their partners must now turn these tentative steps into ambitions strides in order to get ahead of the rising tide of drug resistance before it is too late.

Jayasree K. Iyer
Executive Director
Access to Medicine Foundation

Table of contents

About this report

The 2021 Antimicrobial Resistance Benchmark, which is published by the Access to Medicine Foundation, takes an in-depth look at how the pharmaceutical industry is responding to the challenge of drug-resistant infections. It examines the behaviour of 17 companies with a major stake in the anti-infectives space: eight large research-based pharmaceutical companies and nine generic medicine manufacturers.

These companies are evaluated in areas where they have the greatest opportunity and responsibility to limit antimicrobial resistance (AMR); specifically, research and development (R&D), managing antibacterial manufacturing waste, and ensuring appropriate access to – and responsible stewardship of – antimicrobial medicines and vaccines.

This is the third iteration of the Benchmark, following on from previous reports published in 2018 and 2020. By highlighting where effective action is already being taken, and by showing where not enough is yet being done, the Benchmark's data and analysis can be used as a tool to guide and stimulate pharma companies to tackle AMR.

WHAT WE MEASURE

To assess R&D, the Benchmark focuses in on the eight large research-based companies and their projects that target the pathogens that pose the highest risk of drug resistance, as identified by the US Centers for Disease Control (CDC) and the World Health Organization (WHO).

In terms of responsible manufacturing, all 17 companies were asked to provide information about factories involved in the manufacture of their antibacterial products, with more than a thousand sites reported.

To assess 'appropriate access', the Benchmark looks at all of the companies' actions to improve access to their antimicrobial products in 102 low- and middle-income countries (LMICs). This analysis focuses only on those companies' products which either a) are patented, thus conferring a dominant market position, or b) are off-patent generic medicines with large sales volumes, and are also designated as 'essential' for good functioning health systems by WHO. There are 166 products under analysis.

Finally, all companies are also assessed on their global stewardship policies practices.

HOW COMPANIES ARE SCORED

Each of the 17 pharmaceutical companies has been given both a score and a 'Report Card', detailing their performance since the previous Benchmark and outlining specific opportunities for improvement.

Scoring in the 2021 Benchmark is based on a framework of 20 indicators, which are organised into three Research Areas: Research & Development; Responsible Manufacturing; and Appropriate Access and Stewardship. The Benchmark takes a qualitative and quantitative approach to the data, examining and verifying information provided by the companies in order to reach fair conclusions about their performance.

SECTIONS IN THIS REPORT

Benchmark performance
An analysis of how the 17 companies compare, revealing which companies lead in the Benchmark and why. Large research-based companies and generic medicine manufacturers each come under the spotlight.

Key findings
The three most notable findings from the 2021 Benchmark's research. These cover crucial topics: R&D, access to vaccines and medicines in poorer countries, and safe disposal of antibacterial manufacturing waste.

Research areas and best practice
Four chapters providing in-depth information about the companies' actions in each area, and analysing what the data shows about the pharmaceutical industry. Examples of best practice are featured in order to show what can be done.

Company Report Cards
Set of 17 Report Cards setting out in detail how each of the companies has performed, their official score, and what tangible steps they could take to combat antimicrobial resistance in future.




Executive Summary

The 2021 Antimicrobial Resistance Benchmark evaluates how 17 of the world's largest pharmaceutical companies are performing in the fight against antimicrobial resistance (AMR). These are the companies with the greatest capacity and opportunity to curb AMR, and the Benchmark examines their actions in multiple areas in order to provide a comprehensive picture of what is – and what is not – being done. Many of the companies, consisting of eight large research-based companies and nine generic medicine manufacturers, have moved slowly in the right direction since the previous Benchmark report was published in 2020, despite the ongoing COVID-19 pandemic. But while progress can be seen on some fronts, the Benchmark also identifies concerning gaps in performance.

Why this matters

AMR is a quietly growing, yet deadly, threat. An estimated 750,000 people already die each year due to drug-resistant infections, and unless urgent action is taken, this number will surge over the coming years. Resistance to even 'reserve' antibiotics has increased: 50-70% of the common Gram-negative isolates are now multidrug resistant. At the same time, 5.7 million people die each year from treatable infections due to a lack of access to medicine, compounding the problem as pathogens are given more of a chance to develop resistance.

Antibiotics and other antimicrobials are essential for combatting infectious diseases across the world; if these drugs become ineffective due to resistance – and if replacement drugs are not developed and approved – then the effects on public health will be severe. With the world's attention rightly focused on COVID-19, resistant pathogens continue to emerge and proliferate. The impact of the pandemic on resistance rates is estimated to be considerable, driven by the routine use of antibiotics without appropriate diagnosis in patients hospitalised with COVID-19, and by global disruptions to antibacterial vaccination campaigns.

This 'silent pandemic' can be brought to a halt, and the pharmaceutical industry has a central role to play. The Benchmark tracks, stimulates and guides positive action by highlighting where steps are already being taken, where companies can do better, and where the ecosystem of incentives can be further strengthened.

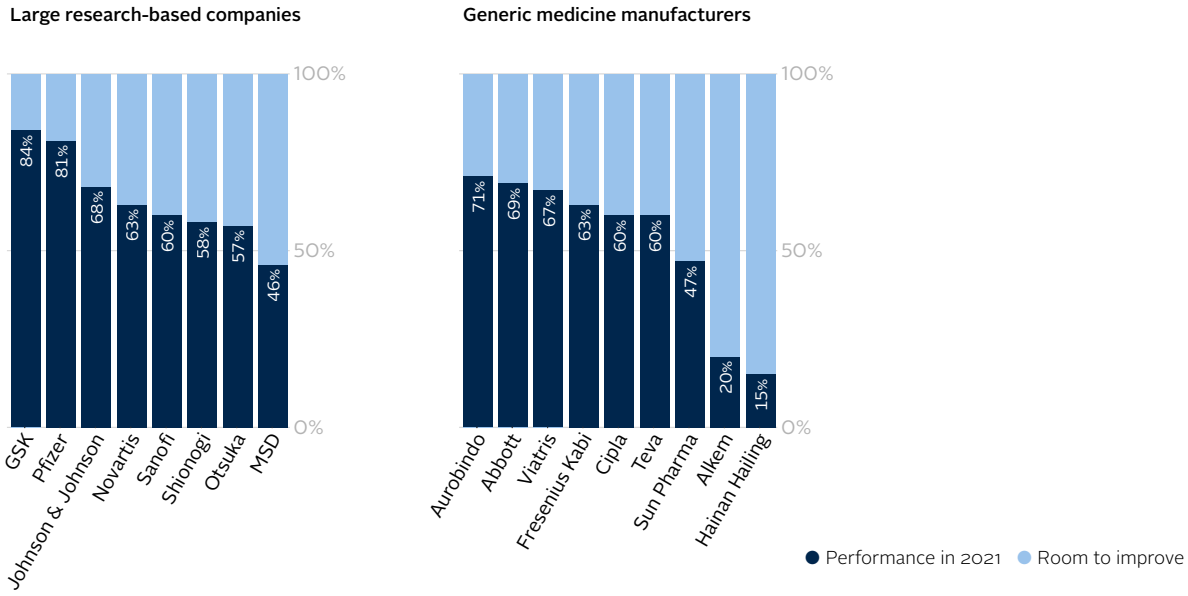
Analysis of industry trends

The Benchmark finds that, while the pipeline of new antibacterials and antifungals remains small, engagement by many large research-based companies' with antimicrobial R&D appears to be growing modestly rather than continuing to shrink. These companies are also improving their forward planning for late-stage medicine and vaccine projects, both in terms of how they will provide access to those products in low- and middle-income countries (LMICs), and how they will safeguard the new products' effectiveness via stewardship strategies.

However, among the 17 companies in scope, there is a lack of momentum in providing access to existing antibiotics and other antimicrobial products in LMICs, where the risk of drug-resistant infections is generally highest. There are many strategies available to pharma companies to improve access to their products in poorer countries, such as tiered pricing, or measures to ensure continuous supply. But as things stand, most access strategies are not being widely used, or remain focused on a small set of countries, people, and diseases.

On the manufacturing side, the Benchmark finds that pharmaceutical companies are

ANTIMICROBIAL RESISTANCE BENCHMARK – 2021 FIGURE 1



making greater efforts to curb the release of wastewater containing active pharmaceutical ingredients (APIs) into local waterways, including by setting and enforcing discharge limits with their third-party suppliers. This is an encouraging step, even though few of their suppliers' factories are – as yet – reported as being compliant with those limits.

Stewardship practices are also improving gradually in multiple areas, such as in sales practices for antimicrobial products, where the first three generic medicine manufacturers have taken steps towards decoupling sales volumes from financial incentives from sales agents.

Which companies are the leaders in 2021?

GSK and Pfizer are joint leaders among the large research-based companies evaluated. GSK has the largest R&D pipeline of any of the companies evaluated, and also performs well in enforcing discharge limits along the manufacturing supply chain. Pfizer has made the biggest strides since the previous Benchmark in the scale and scope of its approach to AMR, including by boosting its infectious diseases R&D, and by demonstrating best practice in multiple areas.

Aurobindo, Abbott and Viatris are the leaders among the generic medicine manufacturers, taking steps to combat overselling of antimicrobials. Abbott and Viatris, alongside Cipla, are also the first of this group of companies to report setting discharge limits at their third-party suppliers' manufacturing sites. Overall, progress by the generic medicine manufacturers can be seen in transparency, stewardship, sales practices, and wider registration of medicines in LMICs.

FINDINGS IN BRIEF

- Only one third (54) of the pharma companies' 166 antibacterial and antifungal products in scope are covered by any 'access strategy' in any of the 102 low- and middle-income countries where better access to antimicrobial products is most urgently needed.

- Some pharma companies are taking tangible actions to improve access to specific products and boost local supply – for example via technology transfers to manufacturing sites in countries including Pakistan, Brazil and Nigeria.

- More pharma companies report that they require third-party suppliers to set discharge limits at their manufacturing sites, but only 5.2% of suppliers' sites are reported as being compliant with these limits. The figure is ten times higher at the companies' directly-operated sites.

- Among the eight large research-based companies, the Benchmark identified 92 R&D projects that target infections caused by 'priority pathogens' – those bacteria and fungi posing the highest risk to human health due to drug resistance. This is a modest increase on 2020, when the same eight companies were developing a combined 77 projects, but the pipeline remains small.

- 18 out of 20 late-stage medicine projects in this analysis have both access and stewardship plans in place, and all 11 late-stage vaccine projects have access plans. There has been sustained progress in this area since the first Benchmark.

- The Benchmark previously reported an increase in the number of pharmaceutical companies that had stopped the use of sales agents altogether, or had decoupled agents' bonuses from sales volume. In 2021, three more generic medicine manufacturers took action to combat overselling: Abbott, Aurobindo and Viatris.

LOOKING AHEAD

Even amidst the ongoing COVID-19 pandemic, the pharmaceutical industry has managed to deliver progress against AMR. One lesson to be learnt from the diverse failures and successes in the fight against COVID-19 is that such a complex global issue can only be tackled through collaborative, coordinated action. With tried and tested policies and practices in the playbook, the pharmaceutical industry must now accelerate its efforts against this global health security threat, with support from policymakers and investors, and through partnerships.

- In R&D, the unwavering priority is for companies to deepen their investment and engagement in antibacterial and antifungal R&D, with a focus on pathogens in the highest threat categories, and to further tailor the detail and specificity of stewardship and access plans.

- In terms of manufacturing, companies must continue to follow through on commitments to good practices, including by extending standards to API and drug-product suppliers. Sharing data on water flows and concentrations will help accelerate the uptake of good practice.

- To deliver appropriate access to life-saving medicines and vaccines, the industry has two core priorities: establish a continuous and local supply of high-quality medicines, and to develop and implement tailored strategies for access to specific products for underserved populations in a wider range of low- and middle-income countries.

- In terms of stewardship, to avoid overuse and misuse of antimicrobial medicines, pharma companies are strongly encouraged to fully and consistently decouple incentives for sales agents from sales volumes, either by avoiding the use of sales agents altogether, or by removing the financial incentive linked to sales volumes. This practice has been pioneered for anti-tuberculosis medicines, and can be successfully transferred.

Top: Sanofi is running tech transfers. GSK adapts packaging to support responsible use. GSK leads in R&D. Bottom: Anti-TB medicines are not promoted by sales staff. Viatris leads in access strategies for TB medicines. Pfizer shares raw surveillance data.

BEST PRACTICES AT A GLANCE

The 2021 Antimicrobial Resistance Benchmark identified best practices in each of its three Research Areas. In the coming months, the Access to Medicine Foundation will work to accelerate their uptake by other pharmaceutical companies, to help raise the level of standard practice.

- **GSK** shows best practice in antibacterial and antifungal R&D, with the largest pipeline of projects that target priority pathogens, including those in the highest threat categories.
- **Pfizer** makes strategic investment in antibacterial and antifungal R&D to get new products to market. It pursues a diverse strategy to maintain and evolve its engagement in R&D.
- **Otsuka** and **Pfizer** set a consistent standard for stewardship and access plans, with comprehensive plans for late-stage projects and strategies tailored to the product.
- **Shionogi** is first to publish the details of its antibacterial waste-management performance, disclosing information on audit results for all antibacterial APIs and/or drug products produced at relevant sites.
- **Pfizer** and **Viatris** use registration to expand availability of on-patent antibiotics, for ceftazidime/avibactam (Zavicefta™) and pretomanid (Dovprela) respectively.
- **Viatris** uses a variety of strategies to improve the affordability and availability of its anti-TB medicines among underserved populations.
- **Ten companies** are involved in technology transfers and other initiatives to enable antibacterial and antifungals medicines and vaccines to be produced locally.
- **Shionogi** remains the only company to fully decouple sales agents' bonuses from sales volumes of antibacterial medicines.
- **Viatris, Otsuka** and **Johnson & Johnson** have stopped their use of sales agents to promote their anti-tuberculosis medicines in order to minimise the spread of resistance.
- **GSK** adapts Augmentin™ packaging to suit a range of patient needs and support its responsible use.
- **Pfizer** remains only company to sharing raw data on AMR surveillance, adding countries and pathogens.

2021 Antimicrobial Resistance Benchmark

The first section of this report provides an overview of how the pharmaceutical companies in scope performed, and whether – and where – progress can be identified.

AMR BENCHMARK PERFORMANCE

- **Trends in pharma company action**
  Pharma shows bright points of progress against AMR, yet lags on access to antibiotics
- **How large research-based companies compare**
  Pfizer makes significant strides to become joint leader alongside GSK
- **How generic medicine manufacturers compare**
  Three new leaders in 2021, as stewardship and access measures increase

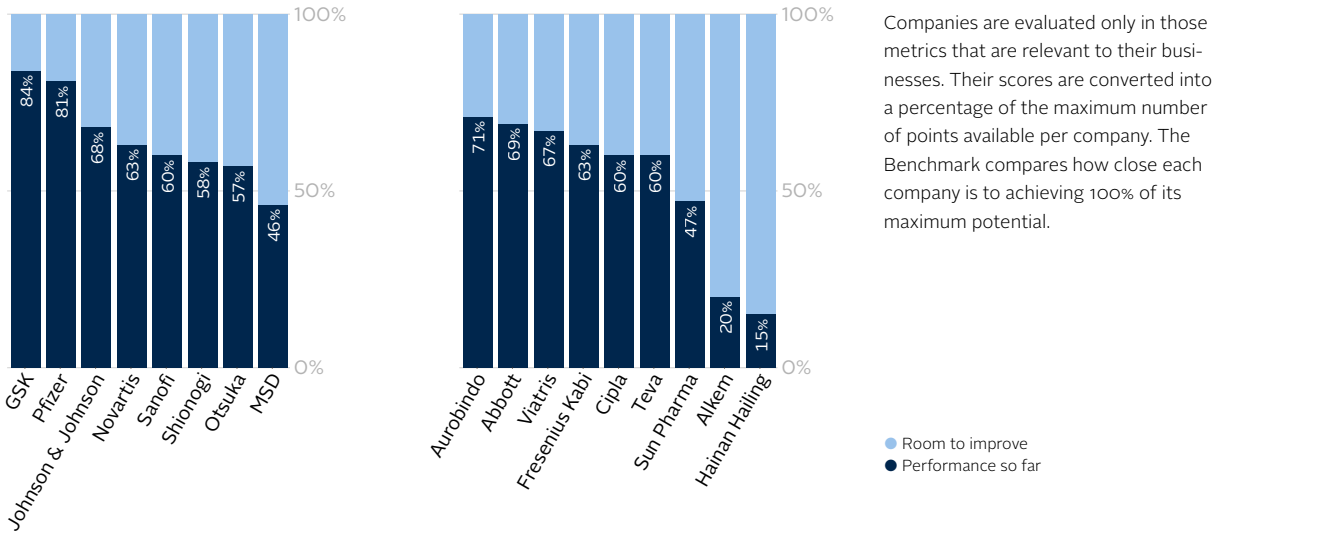
KEY FINDINGS

- **Appropriate Access**
  Pharma companies make limited use of the many ways to improve access to antibiotics
- **Responsible Manufacturing**
  Progress on limiting release of antibiotic waste into environment, but gaps remain
- **Research & Development**
  Increased access and stewardship planning in R&D is hopeful sign for poorer countries

TRENDS IN PHARMA COMPANY ACTION

Pharma shows bright points of progress against AMR, yet lags on access to antibiotics

ANTIMICROBIAL RESISTANCE BENCHMARK – 2021 FIGURE 1



Good practice is becoming more common in the actions taken by pharmaceutical companies to limit the threat of antimicrobial resistance (AMR). This is most notable in the plans to ensure wider access to and responsible use of future products, as well as in the steps taken to curb the release of antibiotic waste into the environment. In stewardship, generic medicine manufacturers are taking a more active role. However, all companies miss opportunities to improve access in low- and middle-income countries (LMICs), where the need is greatest and where people face the greatest threat from superbug infections.

While the antibacterial and antifungal R&D pipeline remains small compared to the scale of the AMR threat, there is a slight increase in projects from the companies evaluated, and there are more projects that target pathogens in the highest risk categories defined by WHO and the US Centers for Disease Control (CDC).* This includes Pfizer's newly acquired antifungal candidate fosmanogepix, which targets pathogens including *C. auris* and potentially represents the first in a new class of antifungals. It also includes GSK's gepotidacin, now in Phase III and the only medicine candidate analysed** that is being tested against *N. gonorrhoeae.* Almost a third of R&D projects target drug-resistant *M. tuberculosis*, which causes the bulk of drug-resistant infections globally. A further third target Gram-negative bacteria, mainly *Enterobacteriaceae*. This includes Johnson & Johnson's *E. coli* vaccine (ExPEC9V), which if successful could prove an important tool for preventing invasive extraintestinal pathogenic *E. coli* disease.

Plans to address the access to and stewardship of new products in countries with high disease burdens have become common, now covering 18 of the 20 medicine candidates in Phase II or beyond. This is a significant improvement since the first Benchmark analysis, published in 2018, when only a handful of projects were covered by plans. Four companies now report policies for access and/or stewardship planning across their whole portfolios. Plans are expanding and becoming more detailed, although quality assessments will be required as projects progress and new products are launched.

* Lists of pathogens identified as R&D priorities due to the threat from AMR have been published by WHO and the US Centers for Disease Control and Prevention (CDC). Both lists use multiple categories to designate risk levels. The highest levels are 'critical' (WHO) and 'urgent' (CDC).

** R&D projects active between 22 June 2019 and 30 April 2021, from the eight large research-based pharmaceutical companies in scope. By volume and value of sales, these are the largest players in the global antibiotics market that are active in innovative R&D today.

More R&D projects target pathogens in the highest risk categories defined by WHO and the CDC.

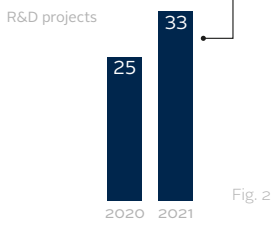


Fig. 2

10 companies now require suppliers to limit the level of antibacterials present in manufacturing wastewaters

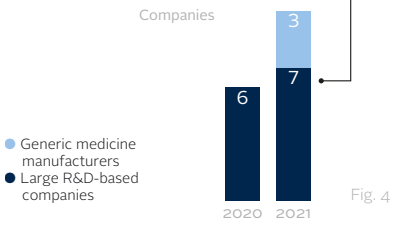


Fig. 4

One third of products assessed are covered by access strategies

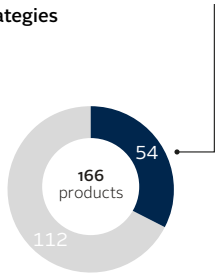


Fig. 6

Almost all late-stage medicine candidates now have both stewardship and access plans

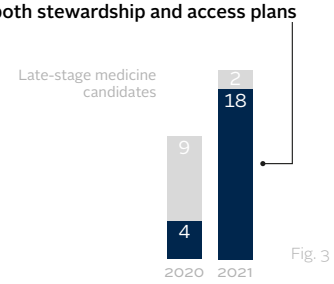


Fig. 3

Companies report discharge levels are under set limits at 13.4% of sites

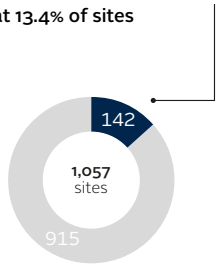


Fig. 5

12 companies now take measures to mitigate the risk of overselling antimicrobials

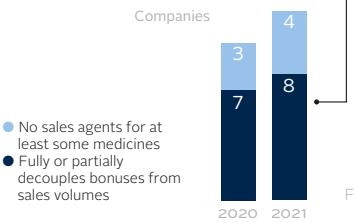


Fig. 7

Companies are doing more to limit the impact of antibacterial manufacturing on drug resistance, including by enforcing good practice with upstream partners. Abbott, for example, has introduced a new template contract for suppliers that specifically require them to meet AMR-related standards. Pharmaceutical companies rely on a large cohort of third-party suppliers for their antibacterial ingredients. The baseline measure, as reported by the companies they supply, is that only 5.2% of third-party sites can be said to be compliant with set limits. Nine companies in scope are actively monitoring levels at own sites, as well as requesting and reviewing per-site discharge levels from third-party suppliers. Shionogi sets the standard for transparency, by publishing detailed information on compliance with set limits at each site. No company has yet insisted that external waste-treatment plants also meet environmental standards relating to AMR.

Companies are improving the availability of products by registering them for sale more widely in LMICs. Viatris,*** for example, has filed its multi-drug-resistant tuberculosis medicine pretomanid (Dovprela) in an additional 23 LMICs since 2020. Nevertheless, the number of filings per country remains low, and this low performance is mirrored in companies' limited use of strategies to improve access to specific products. Only one third of the 166 products assessed are covered by any access strategy in any of the 102 countries assessed. Most products targeted by these strategies are either vaccines, anti-tuberculosis medicines or some of the antibiotics that WHO deems a priority for greater access. As in 2020, pharmaceutical companies are missing many opportunities to make antibiotics available in LMICs.

There are, however, a handful of encouraging examples of industry action that show the direction for improvement. For example, almost all companies take steps to ensure an uninterrupted supply of antibiotics, such as implementing standardised forecasting processes, sharing demand data with stakeholders on a regular basis and establishing global supply networks. Further, ten companies are carrying out technology transfers as a means of boosting supply, including in five countries in Africa: Burkina Faso, Morocco, Nigeria, South Africa and Zambia.

Companies continue to improve stewardship efforts to safeguard the effectiveness of antimicrobial medicines, including how they tackle the risk of overselling. Once again, several companies, including three generic medicine manufacturers, have newly developed or strengthened policies in this area. Aurobindo, Shionogi and Teva go furthest, either by not promoting their products or by fully decoupling bonuses from sales volumes. One company, Cipla, has marginally weakened its policy on sales incentives, although it still goes further than other companies. Progress is clearer in other areas of stewardship, such as in monitoring the spread of resistance.

Companies' surveillance programmes cover a slightly broader range of pathogens on average than previously. Data-sharing has also increased, although there is still only one company, Pfizer, that makes its raw data public. This is despite long-standing commitments from others to take the same step. Actions to mitigate conflicts of interest in educational programmes for healthcare professionals have become standard. This is a big change since 2018, when lines between marketing and educational activities appeared blurred.

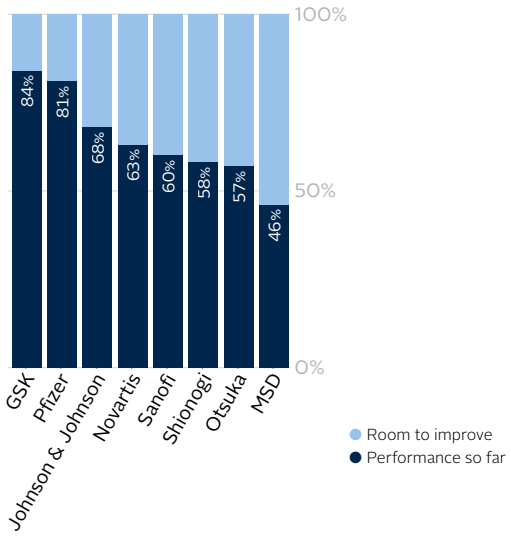
***Formed in 2019 via a merger between Mylan and Upjohn, a division of Pfizer.

HOW LARGE RESEARCH-BASED COMPANIES COMPARE

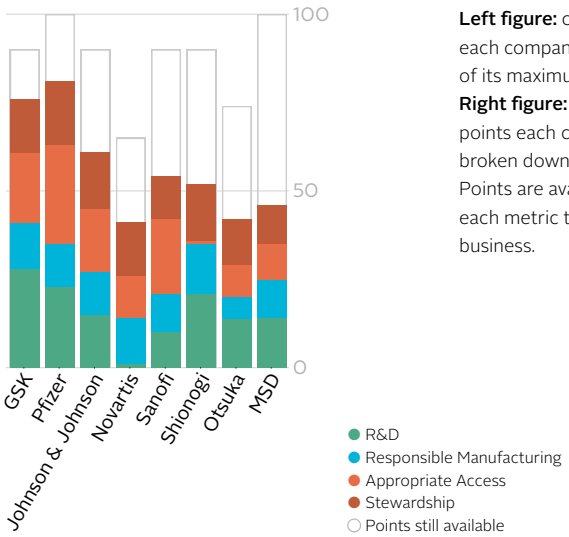
Pfizer makes significant strides to become joint leader alongside GSK

LARGE RESEARCH-BASED PHARMACEUTICAL COMPANIES – 2021 AMR BENCHMARK FIGURE 8

Overall performance - in %



Research Area performance - in points



Left figure: compares how close each company is to achieving 100% of its maximum potential.
Right figure: shows how many points each company achieved, broken down by area of activity. Points are available to companies in each metric that is relevant for its business.

GSK and Pfizer are joint leaders of the large research-based companies in 2021. They are followed by Johnson & Johnson. Although all three leaders perform well across the board, Pfizer made significant improvements in the scale and scope of its efforts to address AMR, and signalled a clear boost to its infectious diseases R&D.

GSK is the clear leader in Research & Development, with 31 R&D projects. About half of its pipeline comprises vaccines projects, the largest number of any company in scope. One third of its projects (11) target pathogens classed as posing a critical and/or urgent threat from AMR, more than any other company. GSK reports access and/or stewardship planning for all of its late-stage projects, and the detail of its reported plans has increased following the implementation of its process for developing such plans in Phase III for all projects. GSK is one of only four companies to report that 100% of its manufacturing sites are in compliance with the discharge limits that it has set. Further, GSK reports that 93% of its suppliers' sites are compliant with discharge limits. It performs less well in stewardship than the other leaders, as it only partly decouples performance incentives for its sales agents from the volumes of sales they can secure.

Pfizer has expanded its R&D pipeline to 13 projects, up from eight in 2020, including those from its acquisitions of the biotechnology companies Arixa Pharmaceuticals and Amplyx Pharmaceuticals. These moves added innovative antibacterial and antifungal projects to its pipeline. Of the companies evaluated, Pfizer has the most late-stage projects that are already covered by plans for ensuring access, including registration commitments and equitable pricing strategies, as

GSK performance by research area

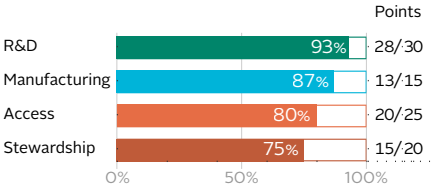


Fig. 9

Pfizer performance by research area

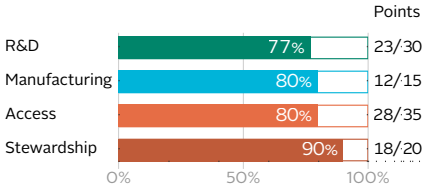


Fig. 10

Johnson & Johnson performance by research area

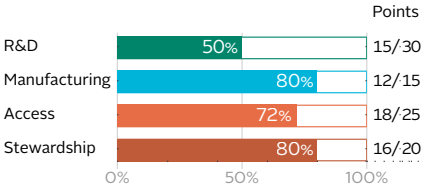


Fig. 11

well as measures to strengthen supply and ensure stewardship. Pfizer stands out for filing its on-patent antibacterial and antifungal medicines across a total of 33 of the 102 low- and middle-income countries in scope for access metrics. This includes a move to file one medicine (ceftazidime/avibactam) in 18 further countries since 2020. Pfizer leads in Stewardship overall, and is the only company that publicly shares raw data from its AMR surveillance programme. It misses out on the top spot as it picks up a smaller proportion of the points available to it than GSK. Nevertheless, Pfizer has demonstrated strong progress in each Research Area.

Johnson & Johnson follows Pfizer. It performs well in all three Research Areas, particularly in Responsible Manufacturing. It reports a comprehensive environmental risk-management strategy for limiting the impact of its manufacturing practices on drug resistance. The company extends the limits it sets at its own sites to its third-party suppliers, proactively reviewing the discharge levels they report. It has a mid-sized R&D pipeline of 14 projects; three more than in 2020. This includes two antibacterial vaccines, including the only vaccine candidate identified that targets *E. coli.* Both WHO and the CDC place resistant *E. coli* in their highest risk categories. Johnson & Johnson employs a range of access strategies to expand access to its on-patent medicine, bedaquiline, in all 30 countries that face a high-burden of multi-drug resistant TB identified by WHO. Yet it provides limited information on access strategies for off-patent/generic medicines.

Novartis performs strongly in Responsible Manufacturing and Appropriate Access, yet has fully retreated from antimicrobial R&D with no projects that target priority pathogens in its clinical pipeline. As a result, it sits in fourth place. It is progressing in access to its off-patent/generic medicines, for example by registering its amoxicillin/clavulanic acid antibacterial in 70 of the countries in scope for the access metrics. Novartis also runs two broad initiatives that aim to expand access to its off-patent/generic medicines, namely the Novartis Access programme and the Novartis Sub-Saharan African (SSA) Unit. In a change since 2020, it now also supports an AMR surveillance programme, running in Poland, which publishes its aggregated results.

Although not in the leadership group, Sanofi, Shionogi and Otsuka each show good practice in specific areas. Sanofi, for example, is taking steps to ensure a continuous supply of its products, including by carrying out technology transfer initiatives in countries such as India, Nigeria, and Vietnam, with the transfer in Nigeria having been supported since 2008. Compared to the other companies evaluated, Shionogi continues to invest the highest proportion of its revenues in antibacterial and antifungal R&D, and is one of only two companies to publish detailed information on which sites, including those operated by third-party suppliers, meet set limits on the concentration of antibacterials in wastewaters. Otsuka, as well as Johnson & Johnson, does not deploy sales agents for its anti-tuberculosis medicine.

MSD* has gained the most approvals of new antibacterials since 2020, but performs less well than its peers as it remains unwilling to share data beyond what is already in the public domain. MSD has published a general commitment to expanding access to its products, but provides little insight into where specifically it has filed its products for registration, or into its strategies to expand access.

These eight companies represent the bulk of the large research-based pharmaceutical companies currently active in infectious diseases R&D. Most of the R&D into antibacterial and antifungal pathogens depends on smaller biotech companies. Nevertheless, the companies evaluated here are conducting R&D that targets pathogens in the highest AMR threat category. The effectiveness of any successful new product must be preserved for as long as possible, which depends on comprehensive access and stewardship plans, but also on growing the pipeline of replacement medicines. As some of the largest producers of antibacterial and antifungal medicines and vaccines, these companies have significant capacity to improve access to their products in the countries with highest need and risk of resistance. Access in low- and middle-income countries can be provided via a range of actions from registering medicines and vaccines to building up the skills, knowledge and expertise needed for local manufacturing, and strengthening supply chains to prevent shortages, while taking each populations' ability to pay into account in pricing policies.

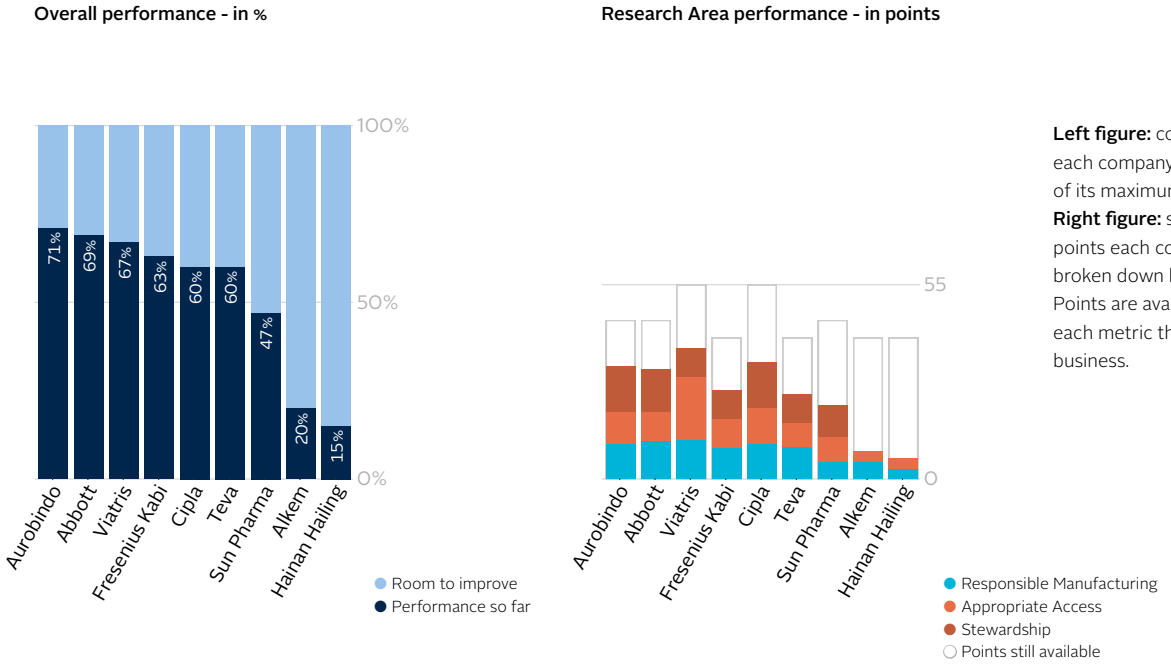
*Merck & Co., Inc (Kenilworth, NJ, United States).

HOW GENERIC MEDICINE MANUFACTURERS COMPARE

Three new leaders in 2021, as stewardship and access measures increase

GENERIC MEDICINE MANUFACTURERS – 2021 AMR BENCHMARK

FIGURE 12



Left figure: compares how close each company is to achieving 100% of its maximum potential.
Right figure: shows how many points each company achieved, broken down by area of activity. Points are available to companies in each metric that is relevant for its business.

Aurobindo, Abbott and Viatris take the lead among the generic medicine manufacturers in 2021. Each of these companies is filing its medicines for registration in low- and middle-income countries, and has improved its sales practices to mitigate the risk of overselling. Abbott, Cipla and Viatris are the first generic medicine manufacturers to report environmental risk-management strategies that apply to their suppliers' sites, as well as their own sites. They also report that they check whether suppliers' sites comply with limits set for environmental standards. Transparency by generic medicine manufacturers has once again increased, amidst the COVID-19 pandemic.

Aurobindo is the overall leader, having progressed significantly in its stewardship measures since 2020. It reports that it does not deploy sales agents to promote its antibacterial and antifungal medicines and ensures that its one educational programme for healthcare professionals mitigates the risk of conflict of interest. As part of its environmental risk-management strategy, Aurobindo not only sets limits but tracks and reports compliance with discharge limits at its own sites. It also requires its two reported third-party suppliers to follow the same limits. Moreover, Aurobindo now discloses more strategies to ensure a continuous supply of its medicines, including steps to prevent shortages.

Abbott has also progressed significantly in its stewardship and manufacturing measures since 2020, including sharing more data. This includes adapting packages to make it easier for patients to follow good stewardship practices. It is also trialling changes to its sales practices in order to limit overselling. In India, it ran a three-month pilot whereby performance

Aurobindo performance by research area

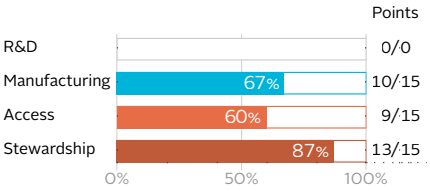


Fig. 13

Abbott performance by research area

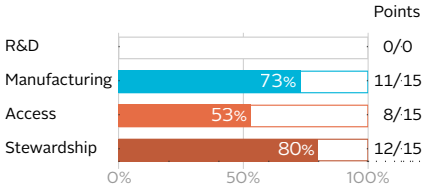


Fig. 14

Viatris performance by research area

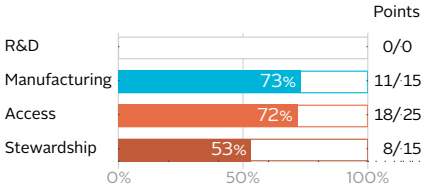


Fig. 15

incentives for its sales agents were decoupled from the sales volumes they could secure for a specific anti-infective product. Abbott performs well in responsible manufacturing, as it now measures the levels of antibacterial residue remaining in wastewater at its own sites to assess compliance with specific limits and extends these standards to some supplier sites. In 2021, it introduced a new contract template for suppliers of APIs and drug products with clauses that require suppliers to implement specific AMR-related environmental standards.

Viatris was formed in 2020 through the combination of Mylan and Upjohn, a division of Pfizer. It performs well with regards to its manufacturing practices as well as its strategies to ensure a continuous supply of products, for example, to address the risk of shortages. It reports that all its own sites are compliant with discharge limits and reports that its ZLD* sites that manufacture antibiotics test recycled waters for the presence of antibacterials, which were found to be zero. It extends its standards and limits to its third-party supplier, and requests and reviews discharge levels as part of audit requirements. Further, it employs conflict of interest mitigation for its AMR-related education programmes for healthcare professionals and is active in two AMR surveillance programmes.

Cipla dropped from leader in 2020 to fifth in 2021 as other companies push forward with improved practices in each of the research areas. It misses opportunities to improve the availability and accessibility in low- and middle-income countries of its on-patent medicine, plazomicin (Zemdri®), which it acquired in 2019. Plazomicin has now been registered in India. However, Cipla does monitor and report the numbers of people it reached with off-patent/generic medicines in India and South Africa during the COVID19 pandemic. In 2020, Cipla had fully removed the link between sales volume and bonuses offered to its sales agents. In 2021, a small portion of its bonuses (1%) have been reconnected with sales volume. Nevertheless, Cipla performs well in Stewardship, and is taking action to limit the impact of its manufacturing operations on resistance. While no longer a member of the AMR Industry Alliance, it sets discharge limits and quantifies the actual levels of antibacterials present in wastewaters at some sites. It has committed to ensuring that it is measuring these levels at all sites by March 2022. Cipla is currently conducting an initial assessment of all suppliers with the intent of extending AMR-related environmental standards to these sites, also by March 2022.

Hainan Hailing and Alkem trail in this group, as they remain the only two generic medicine manufacturers to demonstrate limited transparency. They do not share data that enable the evaluation of their commitment to limiting AMR.

That the generic medicine manufacturers are expanding their efforts against AMR is clear. For the first time, several such companies are requiring their suppliers to meet specific limits on the levels of antibacterials present in wastewaters. Their progress in stewardship is noted in the increased scores, specifically around sales practices, efforts to mitigate the risk of conflict of interest in educational programmes, and in how they adapt product packaging to facilitate stewardship. More of these companies are reporting strategies for improving access to their products in low- and middle-income countries, including to ensure a continuous supply. This is a positive sign, as much more needs to be done.

Pharmaceutical companies have a responsibility to ensure that their medicines are accessible and are reaching those in need. The poorest countries are home to nearly 700 million people and are particularly overlooked by companies' access strategies. Only four generic companies out of nine report that they use access strategies in low-income countries for specific products, and more must be done to improve access to medicines as well as to expand access to vaccines. Generic medicine manufacturers have a responsibility to ensure an uninterrupted supply of good quality products. These companies have an opportunity to improve supply security by implementing strategies such as demand planning and data sharing, and by mitigating against the risk of shortages via sufficient buffer stocks. They can also contribute to scaling up local capacity by supporting local manufacturing hubs and entering technology transfers with originators.

*Zero Liquid Discharge is a waste-treatment process in which no wastewater is disposed into the environment.

KEY FINDING 1: APPROPRIATE ACCESS

Pharma companies make limited use of the many ways to improve access to antibiotics

Vital antibiotics and antifungals are not reaching the populations of poorer countries. Key examples show what pharma companies can do to improve this bleak picture.

- Just one third of products are covered by any access strategy in any of the low- and middle-income countries in scope
- A handful of encouraging examples of pharmaceutical company action suggest possibilities for change

Pharmaceutical companies are not taking the necessary steps to provide access to the antibiotics and antifungals in their portfolios in low- and middle-income countries (LMICs) – and where access strategies are in place, they remain focused on a small set of countries, people, and diseases. However, there are clear and tangible ways that access could be improved, and strategies which could make a real difference to millions of people if deployed more widely.

Why does this matter?

The world's poorest countries experience the greatest rates of infectious disease and the highest levels of antibiotic resistance – but it is precisely these countries that suffer the biggest gaps in access to appropriate medication.

An estimated 5.7 million people, mainly those living in LMICs, currently die each year from lack of access to antibiotics. Unavailability of suitable antibiotics has a huge toll on those directly affected, but is also a hazard for the world, because doctors often resort to suboptimal treatments when the right medicines are unavailable. This gives pathogens an opportunity to develop resistance.

What did the Benchmark analysis find?

The 2021 Antimicrobial Resistance Benchmark examined the access strategies used by pharma companies for a total of 166 established antibacterial and antifungal medicines and vaccines. Of these, only 54 – just one third – are reported to be covered by at least one access strategy in any of the 102 LMICs in scope. The remaining 112 products are either not covered by any access strategy, or the data has not been made available by the companies.

Breaking down those 166 products (see fig, right), only 26% of off-patent/generic medicines are covered by access strategies, compared to 46% of the on-patent medicines. The picture is better for on-patent vaccines, with 72% supported by at least one access strategy – likely reflecting the role of supranational procurement mechanisms such as Gavi, The Vaccine Alliance.

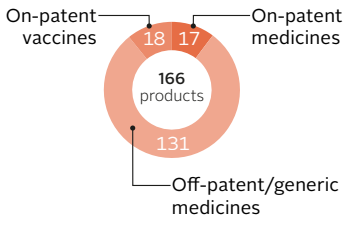
Product registration in local markets is a vital first step in making medicines widely available. There has been incremental progress here, but products are still not widely filed in LMICs. The 2021 Benchmark found only six on-patent medicines had been filed in 10 or more of the 102 countries in scope, including 30 filings for Johnson & Johnson's MDR-TB* medicine bedaquiline, and 25 for MSD's ceftolozane/tazobactam, which is used to treat complicated urinary tract and intra-abdominal infections. These numbers are an improvement from just four products with more than 10 filings in the 2020 Benchmark, but the figures are still too low.

Registration, however, is only part of the story. There are a wide range of tools available to pharmaceutical companies to increase local availability of vital antimicrobials in poorer nations, such as tiered pricing, voluntary licensing agreements, technology transfers, and public-private partnerships. Under certain circumstances, patient assistance programmes and donations can also be used to increase access.

Several companies are showing what can be done in this space. For example, GSK provides access to its antibacterial vaccines through tiered pricing policies and public or private partnerships, including with Médecins Sans Frontières and UNICEF.

FIGURE 16. **What is the data set?**

Across the 17 companies in scope (eight large research-based companies and nine generic medicine manufacturers), 166 products have been selected for analysis. The Benchmark examines the pharma companies' access strategies in relation to 102 low- and middle-income countries, where improved access to medicine is most urgently needed.



* Multidrug-resistant tuberculosis

While the use of technology transfers is limited – with initiatives being undertaken in only 14 of the countries in scope – this approach could be a cornerstone for long-term security of supply and access.

Pfizer is one of the 10 companies with at least one such initiative in place, working with the South African government and Biovac Consortium Cape Town to produce its pneumococcal vaccine Prevnar13® locally, from raw materials to fully released and packaged products.

In terms of medicines, Novartis partners with third parties to produce penicillin products in Pakistan and to transfer manufacturing knowledge – which is significant for patients as penicillin is such a widely-needed antibiotic. Meanwhile, Sanofi has been involved in technology transfers in Nigeria since 2008, enabling a local site to manufacture products including metronidazole (Flagyl®), an antibiotic used to treat a range of conditions from bacterial vaginosis to skin infections.

Access strategies have also been widely used to get tuberculosis medicines to the places where they are most needed. For example, in 2020, more than 125,000 treatment courses of Johnson & Johnson's bedaquiline (Sirturo®) were ordered through Stop TB Partnership's Global Drug Facility, and between 2016 and 2020 at least 25,000 treatment courses of Otsuka's delamanid (Deltyba®) were distributed across more than 80 countries. Viatris is now a generic licensee of delamanid, which will help increase access to this medicine.

What needs to happen next?

The industry needs to reach more people with more products, both old and new. Current industry access strategies do not go far enough, and many of the world's most vulnerable patients are still not receiving the life-saving medicines they need. Future strategies need to increase in quality and reach, in order to cover a wider range of countries, people, and treatments – with the fragments of different strategies coming together to form a more comprehensive picture.

With each medicine or vaccine, pharmaceutical companies should consider the full range of access strategies in the toolkit to work out what is most useful, while always taking affordability into account. This encompasses registering products more widely, including in the poorest countries; further donations and patient assistance programmes; voluntary licensing; entering into partnerships with external stakeholders to increase access; schemes to ensure continuous supply and reduce the risk of shortages; and investing in local capacity-building and technology transfers.

FIGURE 17. **Number of products covered by at least one access strategy, broken down by category**

Of the 166 products examined by the Benchmark, 54 are covered by at least one access strategy. A wide range of strategies count towards this figure, including donations, patient assistance programmes, voluntary licensing, and tiered pricing policies.

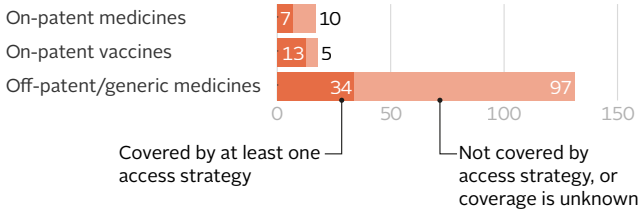
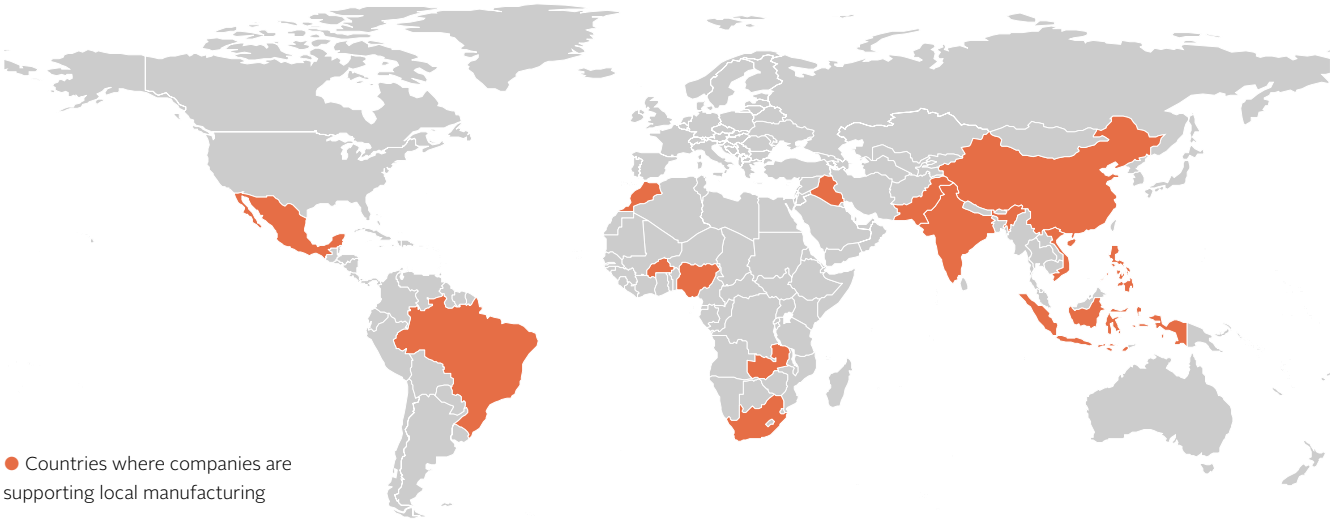


FIGURE 18. **10 pharma companies support local manufacturing projects across 14 low- and middle-income countries**

Of the 17 companies covered by the Benchmark, 10 report that they are supporting local manufacturing (such as by carrying out technology transfers) in at least one of the 102 low- and middle-income countries in scope. This map shows the countries where at least one project is taking place.



KEY FINDING 2: RESPONSIBLE MANUFACTURING

Progress on limiting release of antibiotic waste into environment, but gaps remain

Pharma companies are taking steps to curb the release of antibiotic waste into the environment. They must now go further by consistently setting and enforcing limits at suppliers' sites.

- More companies are setting and enforcing limits at their own sites, and are now starting to expand these standards to supplier sites
- However, just 5.2% of third-party manufacturing sites are reported as compliant with limits on antibacterial waste disposal
- Shionogi and GSK are leading the way in tracking and requiring compliance from suppliers

Pharmaceutical companies are increasingly taking action to limit the release of active pharmaceutical ingredients (APIs) into the environment, by setting and enforcing discharge limits on wastewater from manufacturing sites. While a huge gap remains in ensuring that the same standards apply at manufacturing sites operated by pharma companies' third-party suppliers, progress by a few companies demonstrates that closing this gap is entirely possible.

Why does this matter?

If waste from the manufacture of antibiotics contains a high concentration of APIs when it is discharged into the environment, there is a serious risk it will contribute towards antimicrobial resistance (AMR). While solid waste is typically sent for incineration or to landfill, liquid waste is discharged into environments such as rivers, where APIs can cause bacteria to gain new and dangerous forms of resistance.

In the short term, the release of APIs into the environment poses the most risk to the health of people living near the manufacturing sites. But in the longer term, resistance inevitably spreads and contributes to the global problem.

What did the Benchmark analysis find?

The 2021 Antimicrobial Resistance Benchmark asked 17 large research-based companies and generic medicine manufacturers to disclose the number of sites they and their suppliers use to manufacture antibacterial APIs and drug products, as well as their environmental practices regarding AMR. Fifteen companies provided data about their own sites, and 12 also provided information about their suppliers' sites.*

The picture is most positive at the 187 directly-operated sites under analysis, with large research-based companies reporting compliance at over two thirds of their own manufacturing sites, and generic medicine manufacturers reporting compliance at just over one third of their own sites.

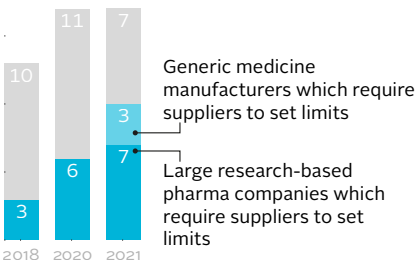
While there has historically been little transparency into how and whether companies work with their suppliers to limit the release of antibacterial waste into the environment at suppliers' sites, clear progress can be identified. The 2018 Benchmark found that only three out of 13 companies required suppliers to set discharge limits,** and this has steadily risen, with 10 companies out of 17 now reporting that they set discharge limits.

However, setting limits only works if companies are tracking and reporting on compliance with these limits. According to the data made available, while limits are set at the majority of suppliers' sites used by those 12 companies (64%), just one fifth of sites measure discharge levels to check for compliance. Only 45 of the 870 suppliers' sites (5.2%) were reported to the Benchmark as compliant.

It is good news that some pharma companies are now working with their suppliers to improve standards, and that

FIGURE 19. **Uptick in companies requiring all suppliers to set discharge limits**

Since the first Benchmark was published in 2018,** there has been an encouraging increase in the number of companies requiring suppliers to set limits on antibiotic wastewater discharge into the environment.



* No data on any manufacturing sites is available for Alkem and MSD. No data on suppliers' sites is avaiable for Fresenius Kabi, Hainan Hailing and Sun Pharma.

** In 2018, the following four companies were not in scope: Abbott, Alkem, Hainan Hailing and Otsuka. They have been in scope of the Benchmark since the 2020 report. The other 13 companies which have remained constant since the 2018 Benchmark are GSK, Pfizer, Johnson & Johnson, Shionogi, Novartis, MSD, Sanofi, Sun Pharma, Cipla, Teva, Fresenius Kabi, Aurobindo, and Viatris (formerly Mylan).

now provides the opportunity to push the remaining 95% of the sites to not only set limits, but to actively monitor and report on compliance.

GSK, for example, reports that antibacterial waste discharges at 37 out 39 of its suppliers' sites are now compliant with set limits. Shionogi has recently made public which of its own sites and suppliers' sites are compliant with limits, and Abbott reports having set enforceable contractual provisions related to environmental standards.

Other leaders on environmental risk-management strategies include Novartis, Johnson & Johnson, and Pfizer, all of which report that they quantify discharge levels against set limits at their own sites, and that they ask their suppliers to set limits and report discharge levels.

The drive to cut waste discharge levels is complicated by the fact that there is currently no internationally-agreed regulation on standards on safe concentrations of antibacterials released into the environment. Instead, companies commit to voluntary targets recommended by the AMR Industry Alliance, which means there is a reliance on self-regulation and self-reporting.

What needs to happen next?

There has been clear movement in the right direction over the last few years as pharma companies increasingly report setting and adhering to limits at their own sites.

Pharma companies must now ensure that limits are set on antibacterial wastewater discharge at all of their suppliers' sites. This is especially important given just how many third-party manufacturing sites are involved in the supply chain (comprising 82% of the total sites covered by this analysis).

Pharma companies should continue to set limits, as well as making sure compliance with these limits is assessed at each site. This must be established via supply contracts and quality agreements, and companies should enforce those agreements when limits are exceeded.

In this way, change will be carried all the way through the supply chain from start to finish, and fewer antibacterials will be discharged into the environment – which would be significant progress in the fight against rising antimicrobial resistance.

FIGURE 20. **Number of manufacturing sites reported as compliant with antibacterial discharge limits**

The first figure shows how many of the 1,057 sites are directly operated by large research-based companies and generic medicines manufacturers, and how many are operated by third-party suppliers. It also shows how the 142 sites reported as compliant are distributed between these three categories. The second figure breaks these raw numbers down into percentages.

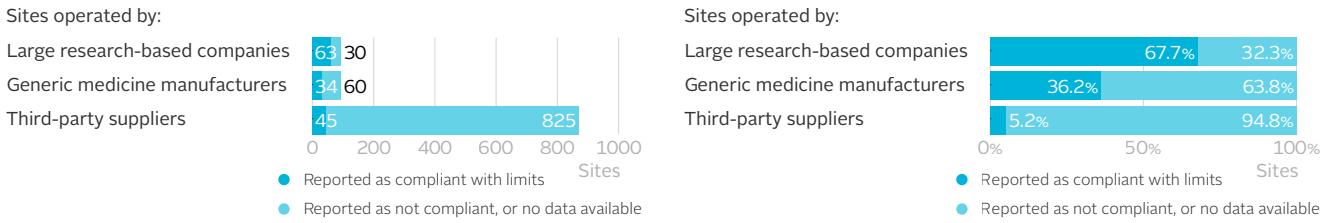
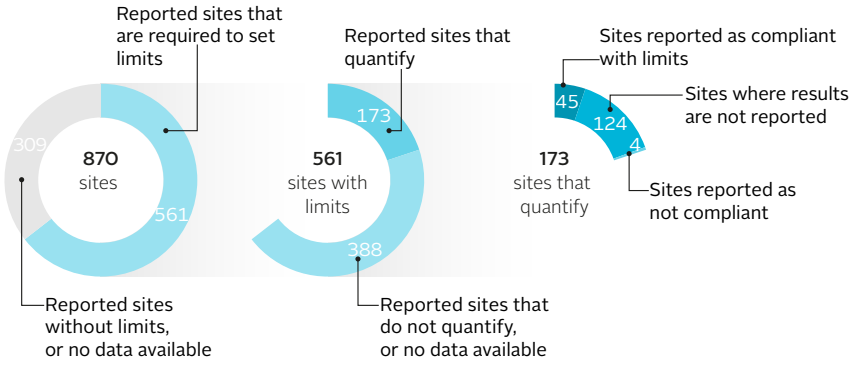


FIGURE 21. **Companies require suppliers to set limits, but many do not assess whether limits are actually achieved**

This figure shows how many sites, out of the total of 870 suppliers' sites, are reported as being required to set limits; how many are reported to quantify discharge limits; and how many are reported as compliant with those limits.



While 561 supplier sites are required to set discharge limits, only 173 of those quantify discharge levels to determine whether limits are exceeded.

That leaves 388 sites where, although limits are being required, no actions are reported as being taken to check whether the actual levels of antibacterial residue in wastewaters are compliant with these levels. This shows that companies need to ensure that discharge levels are actually quantified at all supplier sites.

KEY FINDING 3: RESEARCH & DEVELOPMENT

Increased access and stewardship planning in R&D is hopeful sign for poorer countries

Pharmaceutical companies are making more – and, potentially, better – access and stewardship plans for their future medicines and vaccines.

- ▶ Small R&D pipeline for antibiotics and antifungals means access and stewardship planning is essential for each new product
- ▶ 18 out of 20 late-stage medicine projects in this analysis have both access & stewardship plans in place, a marked increase since previous Benchmarks

Large research-based pharma companies are increasingly treating access and stewardship planning as an integral part of the R&D process, making and sharing plans for a growing proportion of their late-stage clinical projects. There are also signs that these plans are becoming more in-depth and more tailored, which means that new treatments will be more likely to reach people who need them – wherever they live.

Why is this important?

Given the frequent unavailability of medications in many poorer countries, as well as the rising threat of drug resistance, there is an acute need for pharma companies to improve their access and stewardship planning. It is especially important that these plans are baked into the R&D process for new antibiotics and antifungals, for two major reasons.

Firstly, despite some improvements in recent years, there are still not enough products in the pipeline to replace those losing their effectiveness – so it is essential that pharma companies ensure each new medicine is protected from misuse and overuse; and secondly, access to new medicines and vaccines can be life-changing for those suffering the greatest burden of resistant infections. Plans must therefore already be established while any new product is still in clinical development.

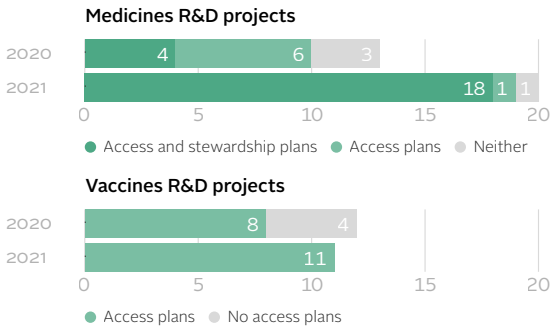
What did the Benchmark analysis find?

The Antimicrobial Resistance Benchmark has closely examined this area since the first report in 2018, when only two of 28 antibiotics in late-stage clinical development had both access and stewardship plans in place. Zooming in on the eight large research-based companies in the Benchmark's scope, there has since been an upward trend, with four out of 13* late-stage medicine R&D projects covered by both access and stewardship plans in the 2020 Benchmark; this rises to 18 of 20 late-stage medicine R&D projects in this latest report.

Companies that have significantly improved their efforts in this area include Pfizer, Otsuka and Shionogi. Pfizer, for example, has added depth and specificity to its plans, which include a wide range of strategies to ensure access in low- and middle-income countries (LMICs), such as filing for registration, equitable pricing, and measures to strengthen supply. Both Pfizer and Otsuka report detailed and varied access and stewardship plans for most late-stage medicine projects in the pipeline. Progress is also seen in the case of Shionogi, which has now signed a Memorandum of Understanding with the Global Antibiotic Research and Development Partnership (GARDP) and the Clinton Health Access Initiative (CHAI) to accelerate access to its late-stage antibiotic cefiderocol for gram-negative bacterial infections in patients with limited treatment options.

The range of stewardship and access plans which the companies intend to enact when their late-stage projects are launched includes registration commitments, potential technology transfers to generics companies, tender agreements to bring down prices, and surveillance programmes.

FIGURE 22. **More stewardship & access plans for late-stage projects**
Among the eight large research-based pharma companies in scope, the Benchmark identifies antibacterial and antifungal projects in late-stage clinical development (Phase II and onwards) that target priority pathogens.** This figure looks at how many of those medicine projects have access and/or stewardship plans in place, and how many vaccine projects have access plans in place (with stewardship not being a concern for vaccines).



* The 2020 Benchmark also included small- and medium-sized enterprises (SMEs) in its scope, so the total figure for all companies was eight out of 32 projects.

** Bacteria and fungi identified as priority R&D targets for limiting AMR by the WHO and/or the US Centers for Disease Control and Prevention (CDC). See Appendix V.

GSK, which has five late-stage R&D projects included in this analysis, employs an equitable pricing strategy framework in LMICs and as part of its Launch Excellence programme. From Phase III onwards, GSK develops launch plans for each market based on disease burden, regulatory requirements, market readiness and market archetype.

Companies behind five of the 11 vaccines in late-stage trials have plans to apply for WHO prequalification and to partner with Gavi, The Vaccine Alliance, to make their vaccines available to the populations that need them most. For example, Sanofi has developed its paediatric vaccine Shan6™ specifically for the LMIC market, with an extensive access plan that includes local manufacturing, equitable pricing strategies, WHO prequalification, and sustainable manufacturing and supply.

Overall, the Benchmark identifies particularly strong access and stewardship plans when it comes to tuberculosis products, supported by consistent proritisation by funders and international organisations. Johnson & Johnson's MDR-TB* medicine bedaquiline has been made widely available through the Stop TB Partnership's Global Drug Facility, and Otsuka is now taking a similar approach by partnering with the Bill & Melinda Gates Foundation as it makes plans for its own late-stage TB candidate.

What needs to happen next?

Pharma companies must make sure that they put access and stewardship plans in place for every single one of their medicines in late-stage clinical development, and that they likewise support their vaccine projects with access plans.

In addition, plans for each new product must become more comprehensive, with companies considering using multiple strategies – and deploying them more widely, with tailoring to local needs. Promising steps in the right direction would then accelerate into strides.

It would also be helpful to see a greater number of products reaching the final stages of the R&D pipeline. In a June 2021 research paper, the Access to Medicine Foundation found that small- and medium-sized enterprises (SMEs) account for 75% of all clinical-stage antibiotics in development and are pivotal in driving new antimicrobial innovation – yet these smaller biotechs often face funding shortfalls and bankruptcy, leaving promising new drugs stranded on the lab bench. As outlined in the report, there is much that large pharmaceutical companies can do to address this problem.**

If and when their late-stage medicines and vaccines reach the market, pharmaceutical companies must follow through and turn their commitments into a reality. That means registering new products in large numbers of LMICs, and executing the access and stewardship plans to the fullest extent.

TABLE 1. **Access and stewardship plans cover a diverse range of strategies**

The table shows the range of strategies that the eight companies are incorporating in their stewardship and plans. The most appropriate strategies depend on the product in question – not all strategies are apprioriate for all products. Companies that have improved their efforts in access and stewardship planning for antibacterial and antifungal medicines include Otsuka, Pfizer and Shionogi.

		GSK	Johnson & Johnson	MSD	Otsuka	Pfizer	Sanofi	Shionogi
Access strategies	Registration	●	●	●	●	●	●	○
	WHO Prequalification Programme	○	○	○	●	●	●	○
	WHO Collaborative Procedure for Accelerated Registration	○	○	○	○	○	○	○
	EMA Article 58	○	○	○	○	○	○	○
	Responsible IP and licensing arrangements	●	○	○	●	●	○	○
	Managed access programmes	○	●	○	●	●	○	●
	Product donation programmes	○	●	○	○	○	○	○
	Special importation waivers	○	○	○	○	○	○	○
	Sustainable manufacturing and supply	○	○	○	●	●	●	○
	Equitable pricing	●	●	○	●	●	●	○
Stewardship strategies	Surveillance	●	●	●	●	●	○	●
	Responsible promotion	○	○	○	○	○	○	○
	Availability of companion diagnostics	○	○	○	●	○	○	○

* Multidrug-resistant tuberculosis

** Biotechs are saving the world from superbugs. Can they also save themselves?, Access to Medicine Foundation, June 2021

Research Areas

The 2021 Antimicrobial Resistance Benchmark looks at companies' performance in terms of R&D, Responsible Manufacturing, and Appropriate Access and Stewardship. The Benchmark's findings are covered in four chapters, each of which lays out the data collected about the companies in scope – and analyses this information to draw out conclusions.

FOUR RESEARCH CHAPTERS

Research & Development

Responsible Manufacturing

Appropriate Access

Stewardship

CONTEXT

Research & Development

As drug resistance rates rise, medicines become less effective, increasing the need for new ones that can replace them. Yet few new antimicrobial medicines have reached the market in recent decades, and the collective pipeline remains small. The World Health Organisation (WHO) and US Centers for Disease Control and Prevention (CDC) have identified drug-resistant bacteria and fungi that pose the greatest threat to human health. These include the superbug *C. difficile*, and carbapenem-resistant *Enterobacteriaceae*, and comprise the priority targets for researchers working in antibacterial and antifungal R&D. The 2021 AMR Benchmark examines the R&D projects that target these pathogens in the pipelines of eight large research-based pharmaceutical companies. The aim is to capture how these companies are supporting global efforts to replenish and protect the antimicrobial pipeline.

KEY CONTEXT

Antimicrobials are at the heart of modern medicine
Antibacterial and antifungal medicines and vaccines are crucial to effective infection prevention and control programmes. Furthermore, antimicrobial medicines also make other procedures and treatments safer, such as surgery, cancer therapy and immunesuppresant treatments.

New medicines and vaccines are urgently needed
Bacteria and fungi can develop drug resistance through the selective pressure imposed by antimicrobials or by sharing genetic material. New medicines are needed to replace those that are losing effectiveness. New vaccines curb resistance by preventing infection in the first place.

Which pathogens are most dangerous?
WHO and the CDC have each published lists of bacterial and fungal pathogens that they view as posing the greatest risk to human health due to resistance.

What is the role for large research-based pharmaceutical companies?
Large research-based pharmaceutical companies have the resources, capacities, and expertise to ramp up antibacterial and antifungal R&D considerably, and to support development by smaller R&D-focused enterprises .

Which companies does the 2021 Benchmark examine in R&D?

The 2021 Antimicrobial Resistance Benchmark examines the antibacterial and antifungal pipelines of eight large research-based pharmaceutical companies. By volume and value of sales, these are the largest players in the global market for antibacterial medicines that are active in innovative R&D today. The Benchmark compares the size and quality of their R&D pipelines. It also looks at the steps these companies are taking to ensure new medicines can be made accessible swiftly yet responsibly for people living in low- and middle-income countries (LMICs), where rates of resistance are highest.

As antimicrobials underpin treatment regimes in many areas of health, these companies have both a business interest in, and a public health responsibility toward, antimicrobial R&D. Furthermore, they have the scale, resources and expertise to support antimicrobial R&D in other ways, for example by partnering with or acquiring smaller companies to help advance their candidates.

Most antibacterial and antifungal R&D is currently being carried out by small- and medium-sized enterprises: 75% of the antibacterial and antifungal R&D pipeline targeting priority pathogens is being developed by such companies. Yet these companies generally lack the financing and other resources, such as regulatory expertise, to commercialise new products. While partnerships with larger companies can help secure the resources they need, several small drugmakers are turning to local companies based in emerging economies, mainly China, to reach global markets.[1]

Which are the pathogens in scope?

The Benchmark focuses on R&D projects that target the priority bacteria and fungi identified by WHO[2] and the CDC[3] as being of particular concern due to drug resistance, for which there is an urgent global need for new treatments.*** There are three levels of prioritisation in the WHO priority list: critical, high, and medium, and four levels of threat in the CDC list: urgent, serious, concerning and watch. Six of the pathogens fall into one or other of these prioritisation categories, including *Candida auris*, one of only two fungal pathogens on either list. Many strains of *C. auris* are proving resistant to all three existing classes of antifungal medicines.

In scope: eight large research-based pharmaceutical companies

	Company	Country HQ
1	GlaxoSmithKline plc	GBR
2	Johnson & Johnson	USA
3	Merck & Co, Inc	USA
4	Novartis AG	CHE
5	Otsuka Pharmaceutical Co, Ltd	JPN
6	Pfizer Inc	USA
7	Sanofi	FRA
8	Shionogi & Co, Ltd	JPN

Priority pathogens: designated by WHO and CDC

Gram-negative bacteria
▲* *Acinetobacter* spp.
B. pertussis
Campylobacter spp.
▲ *Enterobacteriaceae*
E. faecium
H. influenzae type B
H. pylori
M. genitalium
▲ *N. gonorrhoeae*
▲ *P. aeruginosa*
Salmonella spp.
Shigella spp.

Gram-positive bacteria
▲ *C. difficile*
Enterococcus spp.
S. aureus
Group A Streptococcus
Group B Streptococcus
S. pneumoniae

Tuberculosis
M. tuberculosis

Fungal pathogens
A. fumigatus
▲** *Candida* spp.

▲ = Priority pathogens deemed by WHO and the CDC to pose the highest level of concern due to drug resistance ('critical' and/or 'urgent', respectively). Specific resistance profiles can be found in Appendix V.

THE EXAMPLE OF *E. COLI*: WHY NEW TREATMENTS ARE URGENTLY NEEDED

E. coli, a member of the *Enterobacteriaceae* family, is a frequent cause of urinary tract infections (UTIs). These are among the most common infections worldwide, affecting 1 in 2 women at some point in their lives.

→

UTIs are more dangerous for people with diabetes and those undergoing cancer treatment.[4,5]

→

The antibiotic ciprofloxacin is often used to treat UTIs, but resistance is rising – among *E. coli* infections, resistance rates range from 8.4% to 92.2%.[6]

→

E. coli is a gram-negative bacterium, which possesses a dual membrane envelope, making it a challenging target for research into new antibiotics. The Benchmark identified three medicine candidates in clinical development targeting *E. coli* infections specifically.

* *Acinetobacter baumanii* is the species designated as a critical/urgent priority.

** *Candida auris* is the species designated as a critical/urgent priority.

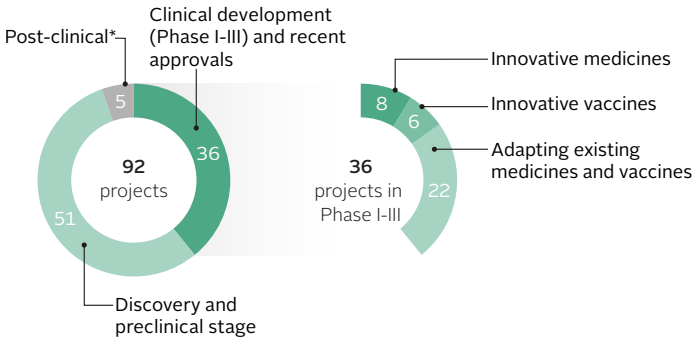
*** I.e., those bacteria and fungi that were identified and prioritised by the WHO in its 2017 Global Priority List of Antibiotic-Resistant Bacteria, and the CDC's 2019 Antibiotic Resistance Threats report. See Appendix V.

RESEARCH & DEVELOPMENT – PIPELINES

Sustained involvement in antimicrobial R&D from seven out of eight companies

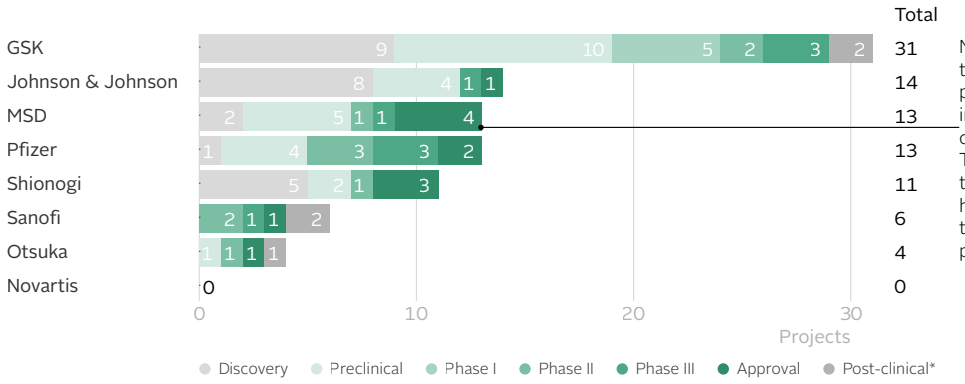
Collectively, the companies evaluated have 92 active medicine and vaccine projects that target infections caused by priority bacteria and fungi. Almost a third of projects target *M. tuberculosis*, which accounts for the bulk of drug-resistant infections worldwide. A further third target gram-negative bacteria, mainly *Enterobacteriaceae*. The majority of projects aim to develop new medicines (62 out of 92). Novartis is the only company evaluated that is not currently active in R&D targeting priority pathogens. The remaining seven companies have sustained their involvement in antimicrobial R&D. Several companies have expanded their pipelines since the 2020 Benchmark report was published. Pfizer and GSK stand out for expanding their pipelines by five and four projects, respectively. GSK leads in R&D, with 31 R&D projects, about half of them vaccines, and including two novel medicine candidates in clinical development. Eleven of its projects target pathogens that WHO and CDC place in the highest risk categories due to AMR.

FIGURE 23. **Eight innovative medicines and six innovative vaccines in clinical development**
Out of the 36 projects in clinical stage, most (22) aim to expand the use of an existing medicine or vaccine to more indications or populations. There are 14 clinical-stage projects that aim to bring new/innovative candidates to the market.



* Post-clinical stages of development (Phase IV or technical lifecycle)

FIGURE 24. **How large are the companies' pipelines – and how far along are the projects?**
Of the eight companies assessed, GSK has the largest R&D pipeline targeting bacteria and fungi in scope. 19 out of 31 projects in their pipeline (61%) are in discovery/preclinical stage.



MSD gained four regulatory approvals during the period of analysis, including relebactam/imipenem/cilastatin (Recarbrio™). This antibiotic can be used to treat a range of serious hospital acquired infections, including bacterial pneumonia.

* Post-clinical stages of development (Phase IV or technical lifecycle)

RESEARCH & DEVELOPMENT – TARGET PATHOGENS

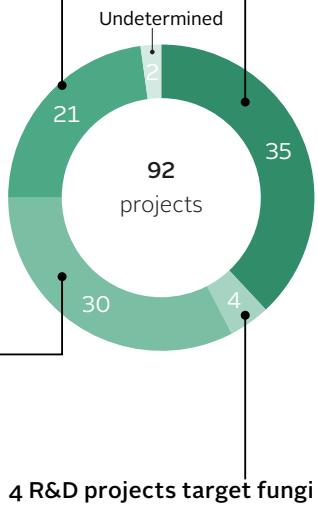
Which pathogens are receiving most attention?

Gram-positive bacteria: empty pipelines for high-risk pathogens

The pipeline for gram-positive bacteria is skewed towards vaccine development, which accounts for 15 of the 21 projects. These most frequently target *S. pneumoniae.* There is currently no medicine candidate in the pipeline targeting this pathogen. The medicines in early-stage development are limited to a handful of projects against *S. aureus*. There is a lack of medicines for *C. difficile*, seen as an 'urgent' threat by the CDC, or for *Enterococcus* spp., seen as a 'high' priority by WHO and a 'serious' threat by the CDC.

Tuberculosis targeted by one third of projects

The projects targeting *M. tuberculosis* represent almost one third of the pipeline, with medicines accounting for 29 of the 30 projects. There is only one tuberculosis vaccine in development by the companies in scope: GSK's M72/AS01E, currently in Phase II. Most of the eight companies evaluated are active in tuberculosis R&D.



4 R&D projects target fungi

There are currently four projects in development against fungal pathogens in scope (*Candida* spp. and *A. fumigatus*). All are in discovery stage, except fosmanogepix, a potential first-in-class antifungal in Phase II development by Pfizer.

Gram-negative bacteria: projects focus on pathogens posing most serious threat

Continuing the trend found in 2020, most of the medicine projects that address gram-negative bacteria target the most critical and urgent threats (27 out of 35)These pathogens are: *Enterobacteriaceae* (including carbapenem-resistant *Enterobacteriaceae*, or CRE, and extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*), *P. aeruginosa* (including carbapenem-resistant and multidrug resistant *P. aeruginosa*) and carbapenem-resistant *Acinetobacter* spp. The projects targeting these pathogens include two recently approved medicines: relebactam/imipenem/cilastatin (Recarbrio™), from MSD, and cefiderocol (Fetroja®/Fetcroja®), from Shionogi. The only vaccine targeting these three pathogens is Johnson & Johnson's ExPEC9V, which targets extraintestinal pathogenic *E. coli*.

The remaining gram-negative pathogens in scope (8) are targeted by just a handful of projects. This includes Sanofi's Shan6™ vaccine for the prevention of *H. influenzae* and *B. pertussis,* and some discovery/preclinical projects targetting *Salmonella* spp. and *Shigella* spp. For some gram-negative pathogens in scope, there are no products in the pipeline: *Campylobacter spp., H. pylori* (both categorised as high priorities by WHO) and *M. genitalium* (on the watch list of the CDC).

PROMISING CANDIDATES

PFIZER

Fosmanogepix

Phase II

Fosmanogepix is potentially a first-in-class antifungal medicine for the treatment of invasive fungal infections, including resistant strains.[7] The ongoing Phase II trial is testing fosmanogepix's efficacy against invasive mold infections caused by *C. auris* or other filamentous fungi.

Stewardship & Access plan: In April 2021, Pfizer acquired Amplyx Pharmaceuticals Inc., and with it fosmanogepix. Pfizer will continue the clinical development of this antifungal as well as the Expanded Access Programme that Amplyx Pharmaceuticals Inc. had put in place.

SHIONOGI

Cefiderocol (Fetroja®/Fetcroja®)

Recently approved

Cefiderocol is a siderophore cephalosporin indicated for the treatment of gram-negative bacterial infections[8] which obtained first approval in November 2019 from the FDA. EMA approval was granted in April 2020.

Stewardship & Access plan: Shionogi has successfully applied for cefiderocol to be included in the WHO's Model List of Essential Medicines (EML), and it has now been placed in the Reserve category of antibiotics. Shionogi has expressed its intention to conduct surveillance for cefiderocol.

Cefiderocol's compassionate use programme is still ongoing. In order to make cefiderocol more accessible, Shionogi reports discussions with generic medicine manufacturers on potential technology transfer options to bring cefiderocol to geographies that their current distribution networks do not reach. In July 2021, Shionogi, the Global Antibiotic Research and Development Partnership (GARDP) and the Clinton Health Access Initiative (CHAI) announced a Memorandum of Understanding (MOU) to accelerate the delivery of access to cefiderocol, including in low- and middle-income countries.[9]

Are projects targeting the most critical and urgent pathogens?

The pathogens targeted most frequently by the eight companies are: CR-/ESBL-producing *Enterobacteriaceae* (14 unique products) and *P. aeruginosa* (8 unique products). Within the *Enterobacteriaceae* family, the focus is on *E. coli* and *Klebsiella pneumoniae*.

Six of the eight companies in scope are developing candidates to target these critical/urgent pathogens, including 18 projects in clinical-stage development or recently approved. GSK leads in this area followed by Pfizer and Shionogi. These three companies have increased the number of their projects targeting critical and urgent priorities since the last iteration of the AMR Benchmark. Three companies are developing vaccines targeting pathogens categorised as critical and/or urgent: GSK (*C. difficile* and *N. gonorrhoea*), Johnson & Johnson (*E. coli*) and Pfizer (*C. difficile*).

Few vaccine projects for gram-negative pathogens

Approximately one third of the pipeline comprises vaccine R&D projects. Vaccines are a critical tool for preventing the spread of infectious diseases, and thereby the development and spread of AMR. Overall, *S. pneumoniae* followed by *Enterobacteriaceae* are targeted by most vaccine candidates in the pipeline. However, very few vaccine candidates target other gram-negative pathogens in scope. This leaves some concerning gaps, such as for *A. baumannii*, an opportunistic pathogen that is associated with hospital outbreaks, as well as for *P. aeruginosa*. Both placed by WHO and CDC in the highest risk categories.

Six of the companies evaluated are developing vaccines (30) for the pathogens in scope. Shionogi is new to this group in 2021, having entered a collaboration with HanaVax to develop a vaccine against *S. pneumoniae*. GSK is developing 16 vaccines, more than any other company. It is followed by Pfizer, with four. Both have clinical-stage vaccine candidates targeting *C. difficile*. These are the only clinical-stage vaccine candidates, alongside GSK's Bexsero (targeting *N. gonorrhoeae)* and Johnson & Johnson's ExPEC9V vaccine (targeting *E. coli)* targeting pathogens in the critical and/or urgent categories.

PROMISING CANDIDATES

PFIZER

C. difficile vaccine (PF-06425090)

Phase III

This innovative vaccine in Phase III would represent the first available vaccine against *C. difficile,* a pathogen categorised as an urgent threat by the CDC. This pathogen causes diarrhoeal disease. Severe, life-threatening cases present mostly in older patients.[10]

Stewardship & Access plan: Assuming regulatory and clinical success, Pfizer would seek to register the product in countries with the highest local burden of disease and explore equitable pricing strategies. Given the lack of data in many countries, particularly LMICs, Pfizer is conducting real world data research studies in several LMICs to strengthen its understanding of burden and unmet need and better assess current burden of disease.

GSK

***M. Tuberculosis* prophylactic vaccine M72/AS01E (GSK692342)**

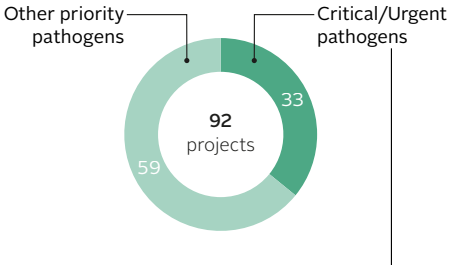
Phase II

This innovative vaccine currently in Phase II trials shows up to 50% efficacy in the prevention of tuberculosis in adults, which is high compared to rates achieved by other candidates.[11]

Access plan: In 2020, GSK licensed the vaccine to the Bill & Melinda Gates Medical Research Institute (Gates MRI). The Gates MRI now leads the candidate development and will sponsor future clinical trials, while GSK will provide the AS01 adjuvant. This agreement increases the likelihood that the candidate is optimised for use in low-income countries and that it is available shortly after approval in countries with a high burden of tuberculosis.

FIGURE 25. **One third of pipeline targets pathogens in highest risk categories**

WHO and CDC each categorise pathogens into multiple tiers to determine the level of risk from AMR. The highest risk categories are 'critical' and 'urgent' respectively.



Critical/Urgent pathogen	Projects
• CR/ESBL-producing *Enterobacteriaceae*	19
• Carbapenem-resistant *A. baumannii*	4
• Carbapenem-resistant *P. aeruginosa*	11
• Drug-resistant *N. gonorrhoeae*	3
• *C. difficile*	3
• *C. auris*	3

FIGURE 26. **One third of the pipeline comprises vaccines R&D projects**

Of the 30 vaccine candidates, 20 are innovative candidates, and 10 aim to establish effectiveness against additional pathogens or serotypes.

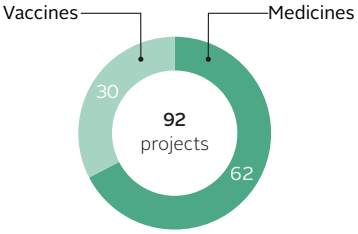


TABLE 2. **92 medicine and vaccine projects target priority bacteria and fungi**

The figure shows how many products are in discovery/preclinical stages and which ones are in clinical development from the eight companies in scope. The pathogens receiving the most attention include *Enterobacteriaceae, S. aureus, S. pneumoniae* and *M. tuberculosis.*

Pathogen	Priority/threat level		Medicines					Vaccines				
	WHO	CDC	Early stages*	Phase I	Phase II	Phase III	Approval	Early stages*	Phase I	Phase II	Phase III	Approval
GRAM-NEGATIVE BACTERIA												
Enterobacteriaceae (CRE/ ESBL-producing)	Critical	Urgent/ Serious	4	FimH (GSK3882347) [GSK]	Avycaz®/ Zavicefta® (neonates) [Pfizer]**; Fetroja®/ Fetcroja® (paediatric) [Shionogi]	aztreonam + avibactam [Pfizer] gepotidacin [GSK]	Recarbrio™ [MSD] Fetroja®/ Fetcroja® [Shionogi]	3			ExPEC9V [Johnson & Johnson]	
Acinetobacter spp.	Critical	Urgent			Fetroja®/ Fetcroja® (paediatric) [Shionogi]		Fetroja®/ Fetcroja® [Shionogi]					
P. aeruginosa	Critical	Serious	5		Avycaz®/ Zavicefta® (paediatric) [Pfizer]**; Fetroja®/ Fetcroja® (paediatric) [Shionogi]		Fetroja®/ Fetcroja® [Shionogi]					
N. gonorrhoeae	High	Urgent				gepotidacin [GSK]					Bexsero [GSK]	
Campylobacter spp.	High	Serious										
Salmonella spp.	High	Serious						3				
H. pylori	High											
H. influenzae	Medium											Shan6™ [Sanofi]
Shigella spp.	Medium	Serious	1					2				
B. pertussis		Watch										Shan6™ [Sanofi]
M. genitalium		Watch										
GRAM-POSITIVE BACTERIA												
Enterococcus spp.	High	Serious				Sivextro® (paediatric) [MSD]						
S. aureus	High	Serious	3			Sivextro® (paediatric) [MSD]	Teflaro®/ Zinforo® (neonates) [Pfizer]**	1	GSK3878858A [GSK]			
S. pneumonia	Medium	Serious						1		Skypac® (Sanofi) V116 (MSD)	Prevnar20™ (paediatric) [Pfizer]	Vaxneuvance™ [MSD] Prevnar20™ (adult) [Pfizer]
C. difficile		Urgent					Dificid® (paediatric) [MSD]		GSK2904545A [GSK]		PF-06425090 [Pfizer]	
Gr. A. Streptococcus		Concerning				Sivextro® (paediatric) [MSD]		1				
Gr. B. Streptococcus		Concerning				Sivextro® (paediatric) [MSD]		1		PF-06760805 [Pfizer]		
TUBERCULOSIS												
M. tuberculosis	AMR R&D priority	Serious	20		GSK-070 (GSK-3036656) [GSK] OPC-167832 [Otsuka] rifapentine + isoniazid (paediatric) [Sanofi]	Rifapentine (new regimen) [Sanofi]	Sirturo® (paediatric) [Johnson & Johnson] Deltyba® (paediatric) [Otsuka]			M72/AS01E [GSK]		
FUNGI												
Candida auris		Urgent	2		fosmanogepix [Pfizer]							
Candida spp.		Serious	2									
Aspergillus fumigatus		Watch	2									

■ There are no projects in the pipeline targeting the pathogens highlighted in grey.

Projects are included for each pathogen that they target, which means some projects are included more than once. Details about specific resistance profiles are in Appendix V.

Adaptations of commercialised products are named with their brand name. Not all projects disclosed to the Benchmark are included in this table due to confidentiality agreements.

*This column displays the number of projects in discovery and preclinical stages of development.
** Teflaro® and Avycaz® are marketed by Allergan in the USA.

RESEARCH & DEVELOPMENT – CHANGES SINCE 2020

R&D pipeline grows slightly, with most companies contributing new projects

With resistance building and medicines becoming less effective, promising clinical candidates are closely watched to see whether and when they are likely to become available. This section examines how the number of R&D projects targeting priority pathogens has changed since the previous analysis,* looking specifically at eight large research-based pharmaceutical companies active in priority pathogens R&D.**

Since the previous Benchmark analysis, 22 projects have left the pipeline, for reasons such as project discontinuation or divestment. But there have been 38 additions to the pipeline. Overall, balancing the 22 projects that have left and the 38 additions, the pipeline has seen a modest increase in size: from 77*** projects to 92 (net increase of 15 projects).

Although the size of the pipeline overall remains small, this upward movement perhaps signals a stabilisation of activity in this area of R&D by large research-based pharmaceutical companies.

Furthermore, one third (18) of the 54 projects that remained in the pipeline from the 2020 analysis have progressed to the next stage of development.** Whether an R&D project progresses along the pipeline depends on multiple factors, including the specific disease being targeted as well as other practical challenges.

Of the 38 new projects that entered the pipeline, 25 are innovative medicines and vaccines. These are important because they may constitute new chemical classes of medicines or incorporate new technologies in vaccine development, and such innovations may prove critical in curbing antimicrobial resistance in the years to come.

FIGURE 27. **R&D pipeline for priority pathogens has grown from 77 to 92 projects**
The eight large research-based companies in scope have added 38 new R&D projects to the pipeline since the previous analysis. There are now 92 projects,*** including some that have recently gained marketing approval, targeting the pathogens that pose the greatest risk from antimicrobial resistance.

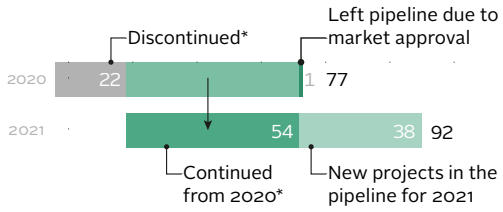
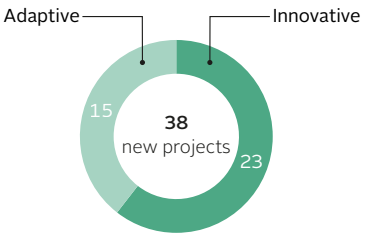


FIGURE 28. **Most new projects are innovative**
Of the new projects that entered the pipeline in this analysis, most aim to develop a new product ('innovative'), rather than establish whether existing ones are also effective for treating additional populations or conditions ('adaptive').



* Since the previous Benchmark analysis, published in January 2020, which covered projects active between 9 September 2017 and 21 June 2019.

** R&D projects from the nine small and medium-sized enterprises that were also assessed in the previous AMR Benchmark report have been removed from the analysis to allow for comparison.

*** This analysis looks at projects active since 22 June 2019 and up until 30 April 2021.

RESEARCH & DEVELOPMENT – NEW MEDICINES

Eight clinical-stage projects aim to develop completely new treatments

The 2021 Benchmark has identified eight clinical-stage antibacterial and antifungal R&D projects that aim to bring to market new chemical entities or new fixed-drug combinations. The hope is that such new treatments are sufficiently different from those agents already on the market that pre-existing mechanisms of resistance will not impair their effectiveness. As such, they are some of the most important projects to watch in the antimicrobial pipeline.

These eight projects comprise four antibacterials, two antituberculosis medicines, one antifungal medicine, and one disclosed on condition of confidentiality. Three of them meet some or all of the innovativeness criteria set by WHO* to identify candidates with high value to combat resistance, for example because they have a new mechanism of action against the target pathogen.[14] The remaining five projects, such as fosmanogepix, which potentially represents a new class of antifungal, do not fall within the scope of WHO's assessment of innovativeness, yet could also provide major therapeutic advances if they reach the market.

The eight projects identified here, if successful, could bolster the antimicrobials arsenal in a few years. Almost all have reached Phase II of development, which is when pharmaceutical companies are expected to start planning how they will bring the new products to people living in low- and middle-income countries, as well as how they plan to safeguard the effectiveness of these medicines with the appropriate stewardship measures. Looking across all clinical-stage projects, GSK, Otsuka and Pfizer are among the companies that most comprehensively develop such plans.

PROMISING CANDIDATES

GSK3882347

GSK

This non-traditional antibacterial medicine is currently in Phase I. It inhibits the *E. coli* adhesive protein, FimH, thus preventing infection by impeding the binding of *E. coli* to the bladder wall.[12] It is indicated for the prevention and/or treatment of UTIs caused by ***E. coli,*** part of the ***Enterobacteriaceae*** family. Some members of this family are resistant to nearly all antibiotics.

OPC-167832

OTSUKA

This is a novel carbostyril derivative with antituberculosis activity as a DprE1 inhibitor.[13] This molecule meets all WHO innovativeness criteria. It is currently in Phase II for the treatment of uncomplicated pulmonary tuberculosis in adults.

TABLE 3. **Potential game-changing antimicrobials in the pipeline**

The table includes two recently approved** medicines and five innovative medicine candidates in clinical development, from five of the eight companies evaluated. An eighth project is not listed, as it was disclosed on condition of confidentiality.

Company	Candidate medicine	Stage	Target pathogen(s)	New drug class	New target	New mode of action	No cross-resistance
MSD	Relebactam/imipenem/cilastatin (Recarbrio®)	First marketing authorisation obtained on 16 July 2019	*Enterobacteriaceae (CRE)*				
Shionogi	Cefiderocol (Fetroja®/Fetcroja®)	First marketing authorisation obtained on 14 November 2019	*Enterobacteriaceae (CRE); Pseudomonas aeruginosa (CRPA); Acinetobacter baumannii (CRAB)*				
GSK	Gepotidacin	Phase III	*Enterobacteriaceae - E. coli*	●		●	
GSK	GSK-070 (GSK-3036656)	Phase II	*Mycobacterium tuberculosis*	●	●	●	●
Otsuka	OPC-167832	Phase II	*Mycobacterium tuberculosis*	●	●	●	●
Pfizer	Fosmanogepix***	Phase II	*Candida auris; A. fumigatum; Fusarium spp.; Scedosporium spp.*	N/A	N/A	N/A	N/A
GSK	FimH (GSK3882347†)	Phase I	*Enterobacteriaceae - E.coli*	N/A	N/A	N/A	N/A

* The four WHO-defined innovativeness criteria for investigational clinical antibacterial candidates are: new chemical class (or structure); new target; new mode of action; and absence of cross-resistance.

** Approved during the period of analysis: from 22 June 2019 to 30 April 2021.

*** As an antifungal, fosmanogepix is not in scope for WHO's Clinical Antibacterial pipeline, but it is considered a potential new class of antifungal.

† This projects is listed in WHO's Clinical Antibacterial pipeline 2020 as a non-traditional approach.

RESEARCH & DEVELOPMENT – APPROVALS

Two new antibacterials and three next-generation vaccines reach the market

Six of the eight large research-based companies in scope have products that received approvals and/or label extensions between the start of the period of analysis, 22 June 2019, and the end of the period of analysis, 24 September 2021. As in the 2020 Benchmark, the majority of these approvals apply to antibacterials already in the market and aim to extend the indications and/or target populations of those products. There have been just two medicines and three vaccines that received first approval since the previous Benchmark analysis. No antifungal medicine has been approved since the start of the Benchmark research programme in 2017. Overall, seven approvals were extensions to allow existing medicines to be used to treat adolescent, paediatric and neonatal patients.

The two medicines that received approval in this Benchmark are: Shionogi's cefiderocol (Fetroja®/Fetcroja®) and MSD's relebactam/imipenem/cilastatin (Recarbrio™). These target *Enterobacteriaceae*, a family of bacteria for which new medicines are urgently needed. Only one other new antibacterial has been approved by the US Food & Drug Administration (FDA) during the period of analysis: lefamulin (Xenleta®) from Nabriva (not in scope).

MSD gained the most approvals: the one mentioned above, one first approval for a vaccine and two label extensions. Shionogi obtained approval for its antibacterial cefiderocol from both the FDA and the European Medicines Agency (EMA).

TABLE 4. **Newly-approved products and label extensions for products already on the market**
The table shows the new approvals and label extensions received by the companies in scope for products targeting priority bacteria and fungi between the start of the period of analysis for the 2020 AMR Benchmark (22 June 2019) and 24 September 2021.

Product name (brand name)	Company	Priority pathogen(s) targeted	Target population	Indication	Approval date by stringent regulatory authority
NEW ANTIBACTERIAL MEDICINES IN THE MARKET					
Cefiderocol (Fetroja®/Fetcroja®)	Shionogi	Enterobacteriaceae; P. aeruginosa	Adults (18+)	Complicated urinary tract infections (cUTIs), including pyelonephritis	14-Nov-19, FDA
Relebactam/imipenem/cilastatin (Recarbrio™)	MSD	Enterobacteriaceae	Adults (18+)	Complicated Urinary Tract Infections (cUTI), including pyelonephritis; Complicated Intra-abdominal Infections (cIAI);	16-Jul-19, FDA
SUPPLEMENTAL APPLICATIONS AND LABEL EXTENSIONS TO PREVIOUSLY APPROVED ANTIBACTERIAL MEDICINES					
Bedaquiline (Sirturo®)	Johnson & Johnson	M. tuberculosis	Adolescent (12-<18 years) and paediatric (5 - < 12 years)	Tuberculosis; MDR-TB	9 Aug 19 and 27 May 20, FDA
Cefiderocol (Fetroja®/Fetcroja®)	Shionogi	Enterobacteriaceae; P. aeruginosa; A. baumannii	Adults (18+)	Gram-negative bacterial infection (aerobic)	23 Apr 20, EMA
		Enterobacteriaceae; P. aeruginosa; A. baumannii	Adults (18+)	Hospital-acquired Bacterial Pneumonia/Ventilator-associated Bacterial Pneumonia (HABP/VABP)	25 Sep 20, FDA
Ceftaroline fosamil (Teflaro®/ Zinforo®)*	Pfizer	S. aureus	Neonatal (birth to less than 2 months of age)	Complicated skin and soft tissue infections (cSSTI)	13 Sep 19, FDA
Delamanid (Deltyba®)	Otsuka	M. tuberculosis	Paediatric (>=30 kg) and paediatric (>=10 kg)	Tuberculosis; MDR-TB	17 Sep 20 and 22 Jul 21, EMA
Fidaxomicin (Dificid®)	MSD	C. difficile	Paediatric (6 months - 18 years old)	C. difficile-associated diarrhea (CDAD)	24 Jan 20, FDA
Relebactam/imipenem/cilastatin (Recarbrio™)	MSD	Enterobacteriaceae	Adults (18+)	Hospital-acquired Bacterial Pneumonia/Ventilator-associated Bacterial Pneumonia (HABP/VABP)	04 Jun 20, FDA
Ceftazidime + avibactam (Avycaz®/ Zavicefta®)*	Pfizer	Gram-negative bacteria	Adults (18+)	Bacteremia	25 Jun 20, EMA
			Paediatric (3 months and older)	Complicated intra-abdominal infection (cIAI); Complicated urinary tract infection (cUTI), including pyelonephritis; Hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP)	17 Sep 20, EMA
NEW VACCINES					
Pneumococcal 15-valent Conjugate Vaccine (Vaxneuvance™)	MSD	S. pneumoniae	Adults (18+)	Pneumococcal disease	16 Jul 21, FDA
Pneumococcal 20-valent Conjugate Vaccine (Prevnar20™)	Pfizer	S. pneumoniae	Adults (18+)	Pneumococcal disease	10 Jun 21, FDA
Shan6™	Sanofi	H. influenzae; B. pertussis	Paediatric	Diphtheria; Haemophilus infections; Hepatitis B; Pertussis; Poliomyelitis; Tetanus	May 21, Indian Regulatory Authorities

*Teflaro® and Avycaz® are marketed by Allergan in the USA.

RESEARCH & DEVELOPMENT – STEWARDSHIP & ACCESS PLANS

In R&D, increased access and stewardship planning for medicines and vaccines

By planning ahead while a product is still in clinical development, pharmaceutical companies can provide swifter access to new products at affordable prices, and have measures in place from day one to ensure new products are used appropriately (known as stewardship). Phase II of clinical development is widely agreed by stakeholders as the point where such planning should start.

Looking at the pipelines of the eight companies in scope, almost all of the medicine candidates that have reached Phase II or beyond are now supported by both stewardship and access plans. This is a significant improvement since the publication of the 2018 AMR Benchmark, when only a handful of candidates were supported. The companies' vaccine projects are now also all covered by access plans (stewardship is not a primary concern for vaccines).

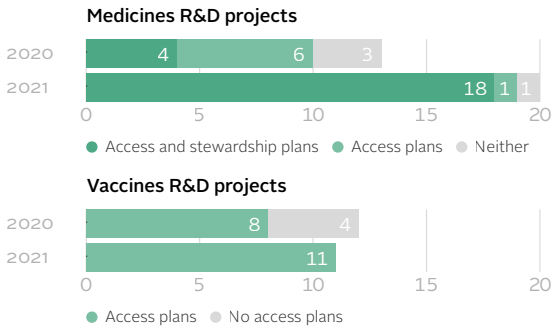
Overall, 18 out of the 20 late-stage medicine projects in this analysis have both access and stewardship plans in place, confirming a trend suggested in the 2020 Benchmark, when the number of projects with both access and stewardship plans rose from two to four. All 11 late-stage vaccine projects have access plans in 2021, a further improvement since 2020, when eight of 12 vaccines had access plans.

There remain big differences in companies' approaches to access and stewardship and how comprehensive their plans are. However, some companies have added more breadth to their portfolio-wide policies on access and stewardship planning since the previous Benchmark. Most companies report project-specific access and stewardship plans for at least some of their projects in late-stage development. The best examples identified by the Benchmark now include a more comprehensive range of access and stewardship measures. Companies are making use of strategies such as affordability frameworks, technology transfers to generic medicine manufacturers, WHO prequalification applications, compassionate use programmes, and the expansion of registration filings, as well as implementing other access provisions stipulated in contractual agreements with funders and partners (e.g., the Global Drug Facility, the Bill & Melinda Gates Foundation, Wellcome Trust, and Gavi, The Vaccine Alliance).

Scope of the analysis
The 2021 Benchmark has assessed whether the eight large research-based companies in scope for the R&D Research Area have access and stewardship plans in place for late-stage candidates (phase II and beyond), how detailed they are and how broadly they are applied.

As with other analyses in this Research Area, the Benchmark focuses on R&D projects that target the priority bacteria and fungi identified by WHO and the CDC as being of particular concern due to drug resistance, for which there is an urgent global need for new treatments.

FIGURE 29. **More stewardship and access plans for late-stage projects**
In 2021, both the medicine and the vaccine late-stage pipelines show an increase in the number of projects with plans to ensure swift access to successful products and to ensure good stewardship of medicines.



Projects funded by organisations, such as the Bill & Melinda Gates Foundation and Wellcome Trust, that request access provisions in their contracts, tend to have stronger, multifaceted access plans. A working group of experts, led by Wellcome Trust and including the Access to Medicine Foundation, have released a Stewardship and Access Plan (SAP) Development Guide[15] that sets out practical actions that pharma companies and product developers can take to develop robust plans early on. The Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) now requires that all grant recipients commit to creating a SAP within 90 days of their product entering pivotal clinical trials (Phase III). Further, grantees are expected to develop a strategy to monitor the effectiveness of such plans.

Among the medicine projects with the most robust plans are Otsuka's OPC-167832 and its paediatric adaptation of the anti-tuberculosis medicine delamanid (Deltyba®). For the latter, Otsuka is building on its experience gained when bringing the adult version of delamanid to market and is taking steps to make the paediatric version rapidly available and suitably formulated for children. A 25mg paediatric dose of delamanid for children has received approval from the European Medicines Agency (EMA). The company is partnering with the Global Drug Facility, generic medicine manufacturers, and children-oriented organisations to develop routes for access, and is donating its product to research institutions to build on its applications. Otsuka's OPC-167832 is also supported by robust access provisions, stipulated through a contractual agreement with the Bill & Melinda Gates Foundation, which co-funds the development of this Phase II anti-tuberculosis candidate.

Also strongly supported by access and stewardship provisions is Pfizer's aztreonam+avibactam. Pfizer has eight late-stage R&D projects targeting pathogens in scope, four medicines and four vaccines, the most of any company evaluated. Pfizer has added depth and specificity to its access and stewardship plans since 2020, which now include a wide range of strategies to ensure access in low- and middle-income countries (LMICs). Pfizer implemented a new policy that went

FIGURE 30. **Which projects are ready for stewardship and access plans?**

A total of 31 projects are in late-stage clinical development and target the pathogens in scope. These projects have reached the stage where companies are expected to start developing access and stewardship plans.

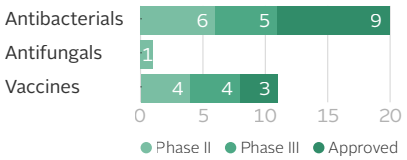


TABLE 5. **Access and stewardship plans cover a diverse range of strategies**

The table shows the range of strategies that the eight companies are incorporating in their stewardship and plans. The most appropriate strategies depend on the product in question – not all strategies are apprioriate for all products. Companies that have improved their efforts in access and stewardship planning for antibacterial and antifungal medicines include Otsuka, Pfizer and Shionogi.

		GSK	Johnson & Johnson	MSD	Otsuka	Pfizer	Sanofi	Shionogi
Access strategies	Registration	●	●	●	●	●	●	○
	WHO Prequalification Programme	○	○	○	●	●	●	○
	WHO Collaborative Procedure for Accelerated Registration	○	○	○	○	○	○	○
	EMA Article 58	○	○	○	○	○	○	○
	Responsible IP and licensing arrangements	●	○	○	●	●	○	○
	Managed access programmes	○	●	○	●	●	○	●
	Product donation programmes	○	●	○	○	○	○	○
	Special importation waivers	○	○	○	○	○	○	○
	Sustainable manufacturing and supply	○	○	○	●	●	●	○
	Equitable pricing	●	●	○	●	●	●	○
Stewardship strategies	Surveillance	●	●	●	●	●	○	●
	Responsible promotion	○	○	○	○	○	○	○
	Availability of companion diagnostics	○	○	○	●	○	○	○

** For products for which these companies are able to make such diagnostics available through its own initiatives or in partnerships.

into effect in May 2020 stating that it will not enforce its patents in least developed countries (LDCs). Furthermore, its late-stage R&D medicine projects fall under portfolio-wide stewardship plans, including initiatives for surveillance and research and education on AMR (via unrestricted grants). For its recently acquired Phase II antifungal, fosmanogepix, Pfizer plans to continue the Expanded Access Programme that Amplyx Pharmaceuticals Inc. had started.

Pfizer's four vaccines are also among the better covered in terms of access plans of the 11 vaccines in late-stage development included in this analysis. These include Pfizer's new pneumococcal 20-valent conjugate vaccine, Prevnar20™ (recently approved for adults), and its vaccines targeting *C. difficile* and Group B *Streptococcus*. The latter is being co-funded by the Bill & Melinda Gates Foundation.

Approved in India in May 2021, Sanofi's Shan6™ vaccine was specifically developed for children in low- and middle- income countries. This vaccine targets six pathogens, adding polio to the group of pathogens previously targeted by the company's Shan5™ vaccine. Sanofi has a dedicated manufacturing facility in India, where it applies supply-chain best practices including buffer and safety stocks. Additional countries in scope for registration include Thailand and Kenya, where there are ongoing Phase III trials. For Shan6™, Sanofi has applied for WHO prequalification to ensure access to the vaccine in all countries eligible for support from Gavi, The Vaccine Alliance. Pooled procurement, for example via Gavi and UNICEF, is an effective route to ensure quality, supported by WHO's prequalification process, and to enable countries to access a stable and affordable supply of vaccines. In addition, Sanofi has developed equitable pricing strategies, conducted a payer pricing survey in nine countries, and takes account of affordability by market type.

With strong company-wide policies for access and stewardship, GSK has five late-stage R&D projects targeting pathogens in scope, and reports having project-specific access plans for most of them. All five projects have ongoing trials in LMICs. GSK does not conduct clinical trials in countries where it does not intend to pursue registration and to make the product available for use. GSK reports that it has developed an equitable pricing strategy framework for LMICs that applies across its portfolio and business units. Its access plans include equitable pricing strategies, registration filings, non-exclusive licensing and supply chain commitments. GSK states that it does not file patents in LDCs or low-income countries nor does it enforce historic patents. GSK commits to conducting global surveillance studies for its new antibacterials to enable appropriate use and support stewardship.

Johnson & Johnson has one vaccine (ExPEC9V) and one medicine in late-stage development, the paediatric adaptation of the antituberculosis medicine bedaquiline (Sirturo®). They are both covered by project-specific access plans. The current stewardship activities ongoing for the adult indication of bedaquiline (Sirturo®) will extend to the newly approved paediatric indication, for use in patients aged 5-12 years and weighing at least 15 kg. There are no clinical trials running for the EXPEC9V vaccine in any of the 102 LMICs examined for this analysis, but Johnson & Johnson is planning to expand its Phase III trial to include LMICs.

Shionogi has progressed in this area by actively seeking out partners to improve access to, and stewardship of, its recently approved antibiotic cefiderocol (Fetroja®/Fetcroja®). MSD does report a general commitment to improving access, through registration and affordability measures, and to ensuring stewardship, primarily through surveillance. Novartis does not have any R&D projects that are eligible for this assessment.

EXAMPLES OF GOOD PRACTICE IN STEWARDSHIP & ACCESS PLANNING

OPC-167832

OTSUKA

OPC-167832 is a novel carbostyril derivative with antituberculosis activity as a DprE1 inhibitor. This molecule meets all WHO innovativeness criteria. The project is currently in Phase II for the treatment of uncomplicated pulmonary tuberculosis in adults.

Stewardship & Access plan: Otsuka is partnering with the Bill and Melinda Gates Foundation in the development of this medicine and the access and stewardship plans for this medicine are in alignment with the BMGF global access requirements.

Aztreonam/avibactam (PF-06947387)

PFIZER

Aztreonam/avibactam is a new fixed-drug combination with activity against carbapenemase-producing *Enterobacteriaceae* (CPE) with metallo-ß-lactamases (MßLs) with Phase III trials ongoing in 11 LMICs.

Stewardship & Access plans: Pfizer is conducting clinical trials in some LMICs. It will explore registration in countries included in the clinical trials and others based on unmet need and disease burden, including countries in Asia and the Middle East among others.

Shan6™ Paediatric hexavalent vaccine DTP-HepB-Polio-Hib

SANOFI

Shan6™ is an hexavalent vaccine targeting diphtheria, tetanus, *B. pertussis,* Hepatitis B*, H. influenzae* type b, and poliovirus.
Poliovirus was added to the 5 pathogens targeted by the Shan5™ vaccine with the aim to reduce the number of shots in children undergoing routine vaccination. Shan6™ is the only project in the pipeline targeting *H. influenzae*. Phase III trials are ongoing in India, Thailand and Kenya, with trials also planned in Vietnam. Sanofi obtained marketing authorisation for Shan6™ in India in May 2021.

Access plan: Shan6™ vaccine is being specifically developed for LMICs and Sanofi has applied for WHO prequalification to ensure access in countres eligible for support from Gavi. Shan6™ will be proposed to Unicef through their tender procurement process and price setting will take into account Gavi's value-based assessment including five premium drivers. Sanofi has a dedicated vaccine facility in India that already successfully produces Shan5™. Sanofi applies supply chain best practices including buffer and safety stocks and shortage mitigation strategies.

Group B Streptococcus vaccine (PF-06760805)

PFIZER

There are ongoing Phase II trials in South Africa for this innovative vaccine. There is currently no vaccine against Group B *Streptococcus (GBS)*, and the development is known to be challenging.
Group B *Streptococcus* is a leading cause of neonatal and young infant sepsis and meningitis, and it is particularly problematic in low-income countries. It is estimated to cause 90,000 infant deaths worldwide annually.[16] Immunisation of pregnant women has the potential of reducing morbidity associated with this pathogen and reduce infant mortality as well as maternal sepsis, stillbirths and preterm births.

Access plan: In 2016, Pfizer received a grant from the Bill & Melinda Gates Foundation to conduct a Phase I-II clinical trial of its vaccine candidate against Group B *Streptococcus* infection in lower- or middle-income countries and is working to develop the vaccine candidate for potential worldwide use.

RESEARCH & DEVELOPMENT

Looking ahead

With antimicrobial resistance on the rise and very few large research-based pharmaceutical companies still engaged in antibacterial and antifungal R&D, it is critical for companies to continue investing in, and developing, these fundamental medicines and vaccines. One lesson to be learnt from the ongoing Covid-19 pandemic is that complex global issues can only be tackled through collaborative, coordinated action. The pharmaceutical industry, policymakers and investors all have a role to play in ensuring R&D efforts address the highest priorities in the fight against AMR.

COMPANIES

Investments and pipeline

- Remain engaged in antibacterial and antifungal R&D, and continue to develop new, innovative and adaptive medicines and vaccines.
- Align investments with global health priorities and direct them towards critical and/or urgent 'priority pathogens'. Be alert and versatile in R&D, moving quickly when the WHO and CDC update their priority lists to include emerging threats.
- Expand focus of pipelines to also target those resistant pathogens for which R&D is limited.

Stewardship and access planning

- Pursue stewardship and access planning for all late-stage clinical projects for new medicines, both novel and adaptive.
- In terms of vaccines, increase access planning and provide swift access to these products in low- and middle-income countries (LMICs). This could have significant impact on curbing the development and spread of resistance.
- Increase the depth and breadth of access and stewardship plans – for example, by expanding schemes into new countries, or by combining multiple types of strategies to increase access to a particular product.
- Take into account the needs of populations in LMICs to ensure new medicines are available in sufficient quantity and quality, and will be appropriately used.
- Ensure stewardship and access plans are inclusive of countries, especially low-income countries, with particularly high burdens of disease and vulnerable populations.

GOVERNMENTS

- Foster a secure and sustainable market for antibiotics and antifungals and develop policies that encourage and incentivise companies to remain engaged in the R&D space.
- Explore new and innovative models, such as pilot programmes for antibiotic and antifungal procurement, delinked from volumes. Ensure selection criteria encourages responsible behaviour from companies.

INVESTORS

- Acknowledge the materiality of AMR and significant risks where untreatable drug-resistant infections could compromise profitable business lines (e.g., cancer medicines and treatments). Engage to support companies in need of investments.
- With new financial incentives for developers of novel antibiotics being piloted by some national governments, make use of opportunities that arise for secure investments in companies leading R&D.

REFERENCES

1. Biotechs are saving the world from superbugs. Can they also save themselves? June, 2021

2. WHO. Global Priority List of Antibiotic Resistant Bacteria to Guide Research, Discovery, and Development of New Antibiotics.; 2017. doi:10.1590/S0100-15742013000100018

3. Centers for Disease Control U. Antibiotic Resistance Threats in the United States, 2019.; 2019. www.cdc.gov/DrugResistance/Biggest-Threats. html. Accessed November 20, 2019.

4. National Cancer Institute. Urinary and Bladder Problems. https://www.cancer.gov/about-cancer/treatment/side-effects/urination-changes.Accessed April 22, 2021

5. Zasloff M. Why are diabetics prone to kidney infections? J Clin Invest.2018;128(12):5213-5215. https://doi.org/10.1172/JCI124922

6. Health Policy Watch. The 'Silent Pandemic' of Antimicrobial Resistance – Lessons Learned From COVID19. https://healthpolicy-watch.newssilent-pandemic-antimicrobial-resistance. Accessed April 12, 2021

7. Shaw KJ, Ibrahim AS. Fosmanogepix: A Review of the First-in-Class Broad Spectrum Agent for the Treatment of Invasive Fungal Infections. J Fungi (Basel). 2020 Oct 22;6(4):239. doi:10.3390/jof6040239. PMID: 33105672; PMCID: PMC7711534.

8. Zhanel GG, Golden AR, Zelenitsky S, Wiebe K, Lawrence CK, Adam HJ, Idowu T, Domalaon R, Schweizer F, Zhanel MA, Lagacé-Wiens PRS, Walkty AJ, Noreddin A, Lynch Iii JP, Karlowsky JA. Cefiderocol: A Siderophore Cephalosporin with Activity Against Carbapenem-Resistant and Multidrug-Resistant Gram-Negative Bacilli. Drugs. 2019 Feb;79(3):271-289. doi: 10.1007/s40265-019-1055-2. PMID: 30712199.

9. GARDP, CHAI and Shionogi announce MOU to increase access to antibiotic to treat antimicrobial resistant infections in low- and middle-income countries [Internet]. GARDP. [cited 2021 Nov 9]. Available from: https://gardp.org/news-resources/gardp-chai-shionogi-announce-mou/

10. Jump RL. Clostridium difficile infection in older adults. Aging health. 2013;9(4):403-414.doi:10.2217/ahe.13.37

11. Tait DR, Hatherill M, Van Der Meeren O, Ginsberg AM, Van Brakel E, Salaun B et al. Final analysis of a trial of M72/AS01E vaccine to prevent tuberculosis. N Eng J Med. 2019;381(25):2429–39 (https://pubmed.ncbi.nlm.nih.gov/31661198/, accessed 5 August 2020).

12. CARB-X funds GSK to develop a new drug for urinary tract infections (UTI) caused by Escherichia coli bacteria: CARB-X [website] Boston: Boston University; 2021 (https://carb-x.org/carb-x-news/carbx-announces-funding-for-gsk-to-develop-a-new-drugfor-urinary-tract-infections-uti-caused-by-escherichiacoli-bacteria/, accessed 23 January 2021).

13. Hariguchi N, Chen X, Hayashi Y, et al. OPC-167832, a Novel Carbostyril Derivative with Potent Antituberculosis Activity as a DprE1 Inhibitor. Antimicrob Agents Chemother. 2020;64(6):e02020-19. Published 2020 May 21. doi:10.1128/AAC.02020-19

14. 2020 Antibacterial agents in clinical and preclinical development: an overview and analysis. Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO.

15. Stewardship & Access Plan (SAP) Development Guide. 2021 [www.carb-x.org/about/stewardship-and-access]

16. Davies HG, Carreras-Abad C, Le Doare K, Heath PT. Group B Streptococcus: Trials and Tribulations. Pediatr Infect Dis J. 2019 Jun;38(6S Suppl 1):S72-S76. doi: 10.1097/INF.0000000000002328. PMID: 31205250

CONTEXT

Responsible Manufacturing

A huge number of manufacturing sites around the world are involved in the production of antibacterials, with many based in India and China.[1] If these sites do not manage their waste appropriately, the discharge of wastewaters containing active pharmaceutical ingredients (APIs) into the environment may lead to the development of resistant bacteria, or the emergence of new forms of resistance which existing medications cannot effectively treat.[2,3,4] It is therefore critical that companies take responsibility for, and are cautious about, their manufacturing processes.[5,6]

Companies that operate manufacturing sites can reduce the risk of antimicrobial resistance (AMR) by implementing a robust environmental risk-management strategy. This governs how sites manage and dispose of waste that potentially contains APIs, including by auditing and monitoring to ensure the levels of antibacterial residues present in wastewaters do not exceed limits that are considered safe. Pharma companies can leverage their positions in the supply chain to raise standards at suppliers' sites by requiring them to meet specific limits, and by extending those standards to the waste treatment plants they contract to dispose of manufacturing waste.

Companies and products in scope

Seventeen pharmaceutical companies – made up of 8 large research-based companies and 9 generic medicine manufacturers – are in scope for the 2021 AMR Benchmark, with a combined total of 801 antibacterial products.

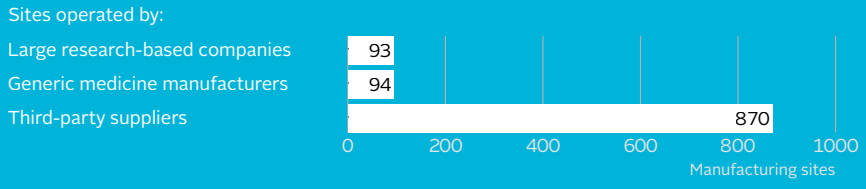
Manufacturing sites in scope

The Benchmark examines the pharma companies' policies and practices with regards to a combined total of 1,057 antibacterial manufacturing sites, based on data reported by the companies.* Together, their antibacterial manufacturing sites consist of:

- 93 sites operated directly by large research-based companies
- 94 sites operated directly by generic medicine manufacturers
- 870 sites operated by third-party suppliers to the companies in scope

FIGURE 31. **Majority of manufacturing sites in this analysis are operated by suppliers**

This figure shows the number of sites in scope of the analysis, broken down by whether they are operated by large research-based companies, generic medicine manufacturers, or third-party suppliers.

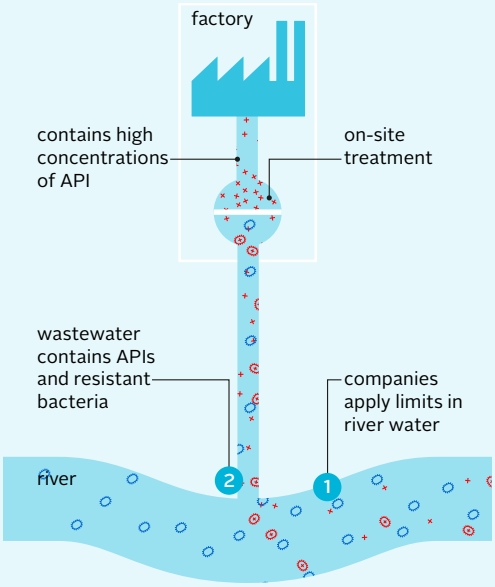


* No data on directly-operated sites is available for two companies: Alkem and MSD. No data on suppliers' sites is available for five companies: Alkem, Fresenius Kabi, Hainan Hailing, MSD and Sun Pharma.

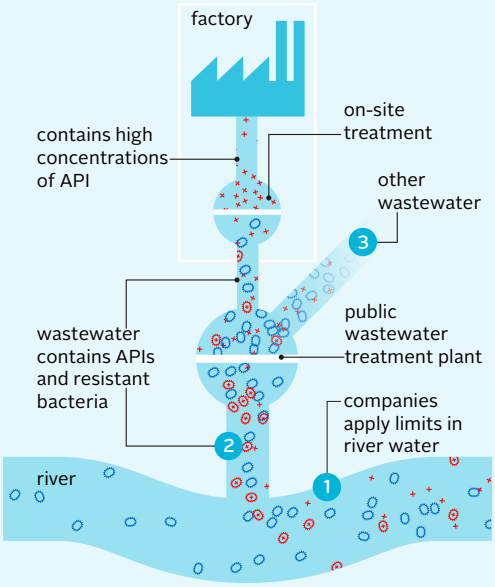
TWO TYPICAL WAYS ANTIBACTERIAL WASTEWATER IS DISCHARGED INTO THE ENVIRONMENT

Antibacterial manufacturing sites produce wastewater which contains active pharmaceutical ingredients (APIs). These diagrams demonstrate two of the most common ways in which those wastewaters are discharged into the environment, for example into a river near the manufacturing site.

OPTION 1. **Wastewater is directly discharged into the environment**



OPTION 2. **Wastewater is sent to a public wastewater treatment plant, before being discharged into the environment**



bacteria APIs resistant bacteria

1 While solid waste containing antibacterials is typically sent for incineration, liquid waste is discharged into the environment. As recommended by the AMR Industry Alliance, companies generally assess whether they have met limits by calculating concentrations in the receiving environment (e.g. the river) rather than directly in the wastewater leaving the manufacturing site after on-site treatment. As such, the wastewater will often be strongly diluted at the point where limits are applied.

Applying limits directly to the wastewater before it is discharged into the environment would be a more desirable approach in the fight against rising AMR. This is because selection of antibiotic-resistant bacteria can still occur in the wastewater itself, due to the presence of bacteria and high concentrations of antibacterials.[5,7–12] In addition, if wastewater containing high levels of APIs is sent to public wastewater treatment plants, it also poses a risk as these plants are known hotspots of selection for resistance.[13,14]

2 When companies treat wastewater on-site, especially using biological methods, many bacteria will still be present in the wastewater, leading to the risk of resistance.

3 It is important to note that public wastewater treatment plants also receive other wastewater from municipalities, which can contain high levels of bacteria but also antibacterial residue as result of human use.[15]

RESPONSIBLE MANUFACTURING – SUPPLY CHAIN STRATEGIES

Self-regulation is the basis for companies' environmental risk-management strategies

What does the Benchmark assess?

The Benchmark looks at whether companies' environmental risk-management strategies include:

- Management systems and treatment practices, including details of techniques and processes to collect and treat both solid waste and wastewater;
- Details on plans for periodic audits for sites, including how to identify problematic processes and to initiate corrective and preventive action (CAPA, see right);
- Defined limits, set specifically for the maximum levels of antibacterial residue present in waste/wastewaters, such as predicted no-effect concentrations (PNECs, see right);
- Details on plans for risk assessments and monitoring of discharge levels at all sites, so that compliance with set limits can be assessed.

It is critical that pharmaceutical companies implement strategies at their own sites, as well as requiring their suppliers and waste-treatment contractors to meet the same environmental standards.

How wastewater limits and targets have been established

Of the 801 antibacterial products in scope, 688 (86%) have an established science-based PNEC target laid out in the recommended list by the AMR Industry Alliance. In February 2021, a default value was added to the list for those active ingredients which do not have a specified target as of yet.[19]

Twelve of the 17 companies apply the PNECs as voluntary targets. However, there are currently no legally binding limits for antibacterial discharge from manufacturing. This means there are no legal consequences for companies when targets are not achieved. Responsibility lies with governments to develop a regulatory framework with limits for emissions of antibacterial waste, in order to incentivise action when safe levels are not met.

How levels of antibacterials are quantified by companies

Rather than measuring antibacterials in wastewater samples, it is common practice for companies to calculate the final concentrations in the receiving environment. This is also known as the mass balance approach and consists of:

- Estimating how much of the antibacterial ingredient is lost in the production process and will end up in waste, i.e. the mass balance;
- Estimating how much antibacterial residue is removed by on-site treatment (and other treatment plants if applicable);
- Applying dilution factors due to water flows from treatment plants and rivers, if applicable.

Nine of the 17 companies report that, only when deemed necessary, mass balance calculations are verified by sampling wastewater and performing chemical analysis. This verification is helpful to make sure the approach used for calculations is accurate, or to check whether calculations are correct and whether limits have truly been met or exceeded.

KEY TERMS

Environmental risk-management strategy
A strategy developed specifically to minimise the impact of manufacturing processes used at a manufacturing site on the environment, and to address the associated risk of AMR.

Corrective and preventive action (CAPA)
A set of actions or improvements which can be implemented by a company in order to tackle non-compliance, and to make sure these issues do not occur in future.

Predicted no-effect concentration (PNEC)
The highest estimated concentration at which no adverse effects on the environment, such as the opportunity for resistance selection or harm to aquatic life, are expected to occur.[16,17,18]

The role of the AMR Industry Alliance

The AMR Industry Alliance is a coalition of pharmaceutical companies formed in 2016 to deliver on the commitments made in the Davos Declaration on curbing AMR.

Twelve of the 17 companies in scope have made a public commitment to assess their own and suppliers' sites through the AMR Industry Alliance's Common Antibiotic Manufacturing Framework (CAMF). These companies include all the large research-based companies in scope, as well as the generic medicine manufacturers Aurobindo, Fresenius Kabi, Teva and Viatris. CAMF is a publicly available tool that provides strategic recommendations on handling and treatment of antibacterial waste, risk assessment, and auditing to minimise AMR risk from antibacterial manufacturing. [21]

As implementation is an ongoing process, long-term action plans need to be developed and tailored by each company.

TABLE 6. **Depth and breadth of environmental risk management strategies**

As in 2020, the 2021 Benchmark looks at whether companies' environmental risk-management strategies include audits, limits and quantification of antibacterial discharge (depth), as well as examining where and how companies apply these strategies (breadth).

	Own manufacturing sites		Third-party suppliers of APIs and/or drug products		External private waste-treatment plants	
	Strategy & audits	Limits & quantification	Strategy & audits	Limits & quantification	Strategy & Audits	Limits & quantification
●	● Strategy to limit AMR adopted, including audits and CAPA	● All sites have quantified discharge levels against set limits	● Strategy adopted by suppliers, including audits and CAPA	● Suppliers asked to set limits and report discharge levels	● AMR-specific audits of private plants*	● Private and/or public wastewater plants asked to set limits and report discharge levels
●		● Company has set limits but not all sites have quantified discharge levels	● Strategy not fully adopted by suppliers and supplier audits not performed yet	● Suppliers asked to set limits; unclear how levels are assessed	● General audits of private plants only	
○	○ No or limited evidence that the company fulfills the corresponding element					
Large research-based pharmaceutical companies						
GSK	●	●	●	●	●	○
Johnson & Johnson	●	●	●	●	●	○
MSD	●	●	●	●	●	○
Novartis	●	●	●	●	●	○
Otsuka	○	○	○	○	○	N/A
Pfizer	●	●	●	●	●	○
Sanofi	●	●	●	●	●	○
Shionogi	●	●	●	●	●	N/A
Generic medicine manufacturers						
Abbott	●	●	●	●	●	○
Alkem	○	○	○	○	○	○
Aurobindo	●	●	●	**	●	○
Cipla	●	●	●	●	○	○
Fresenius Kabi	●	○	○	○	○	○
Hainan Hailing	○	○	○	○	○	○
Sun Pharma	○	**	○	○	○	○
Teva	●	●	●	○	○	○
Viatris	●	●	●	●	○	○

SANOFI

Sanofi implemented a Health Safety and Environment management system (HSE) and Pharmaceuticals In the Environment (PIE) programme. These include environmental requirements intended to minimise the impact of the discharge of antibacterials on the environment.

VIATRIS

Zero liquid discharge (ZLD) technology is a treatment process in which the site does not discharge any water into the environment as this will be reused and recycled, while solid residue is incinerated or sent to landfill after treatment.[21] Of the five companies which currently implement ZLD, Viatris is the only company to report that it has taken the extra step of analysing the recycled water to check for the presence of APIs, which was found to be at zero.

SHIONOGI

Shionogi's sole directly-operated manufacturing site is located in Kanegasaki, Japan, and this is where it manufactures five out of its eight antibacterial products. The three remaining medicines are produced by third-party suppliers. For Shionogi's products, five of its APIs have an established science-based PNEC. For those APIs without a specific PNEC, Shionogi applies a default value of 0.01 µg/L. Shionogi has set the expectation that its suppliers must also follow these limits.

* The Benchmark looks whether audits assess if waste treatment plants have in place: 1) suitable technologies to treat, store and dispose antibacterial waste, as applicable; 2) protocols to prevent contamination of antibacterial waste in soil, surface and groundwater, as applicable.

** Company indicates all applicable sites are ZLD. It is unclear how the company assures these sites are not a risk for AMR – for example, whether recycled water is analysed for the presence of antibacterials.

N/A indicates the company does not make use of any private or public wastewater treatment plants.

RESPONSIBLE MANUFACTURING - SUPPLY CHAIN STRATEGIES

Companies increasingly require their suppliers to set discharge limits

Antibiotic manufacturing chains are sprawling and complex, with many different suppliers delivering active pharmaceutical ingredients (APIs) and drug products to downstream partners. Pharmaceutical companies, including both large-research based companies and generic medicine manufacturers, occupy dominant positions in these supply chains as the suppliers' major customers, and are therefore uniquely placed to influence the standards and practices of those upstream suppliers.

The Benchmark firstly examines whether pharmaceutical companies implement ambitious AMR risk-management strategies and standards at their own sites, and then examines whether they require their suppliers and waste treatment plants to also meet the same standards.

Limits are set out in companies' environmental risk-management strategies, and indicate the highest acceptable level of antibacterial residue which should be present in antibacterial manufacturing waste when released into the environment.*

Progress in requiring suppliers to set limits

Companies generally perform the best at setting and monitoring specific AMR-related standards at their own manufacturing sites, as can be seen in Table 6. However, there is progress in requiring suppliers' manufacturing sites to also meet specific standards around limits on the levels of antibacterial residue in wastewater.

All assessed large research-based companies now report that they require suppliers to set discharge limits, except for Otsuka. Since the 2020 Benchmark, Sanofi newly reports requiring its suppliers to set limits.

In the previous two iterations of the Benchmark, no generic medicine manufacturers reported that they required suppliers to set limits. Now, for the first time, the Benchmark can report that three generic medicine manufacturers require suppliers to set limits, namely Abbott, Cipla and Viatris. Abbott, for example, introduced a new contract template for suppliers in 2021, with clauses that specifically require implementation of AMR standards. If corresponding audit results are not satisfactory, Abbott can enforce contractual provisions.

Looking at the other generic medicine manufacturers, Teva has future plans in place to assess suppliers and require them to set limits. Fresenius Kabi encourages suppliers to set limits – but formal mechanisms such as audit requirements or specific terms in supplier contracts, are not in place.

FIGURE 32. **Uptick in companies requiring all suppliers to set discharge limits**

Since the first Benchmark was published in 2018,** there has been an increase in the number of companies requiring suppliers to set limits on antibiotic wastewater discharge into the environment.

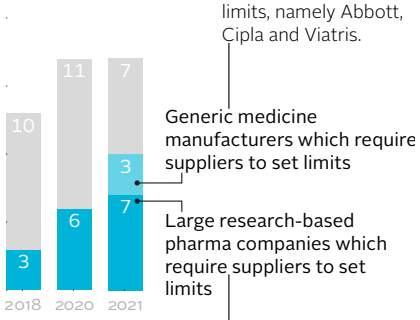
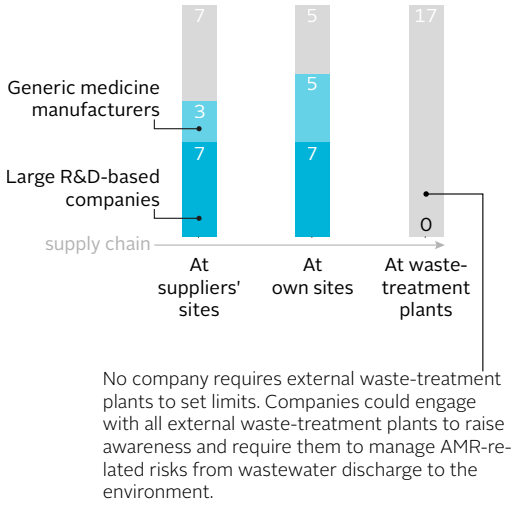


FIGURE 33. **How far do discharge limits apply along the supply chain?**

This chart shows how many of the companies apply discharge limits along the supply chain.



* When companies report sites as compliant with limits, it means the estimated concentration in the receiving environment is safe, not in the wastewater leaving the manufacturing site itself.

** In 2018, the following companies were not in scope: Abbott, Alkem, Hainan Hailing and Otsuka. They have been in scope since the 2020 Benchmark.

RESPONSIBLE MANUFACTURING – COMPLIANCE WITH LIMITS

Reported compliance with limits lags behind, especially at suppliers' sites

As the number of sites that set limits to mitigate the risk of AMR increases, the next step is to examine whether these limits are achieved in practice. The Benchmark surveyed the 17 companies in its scope to assess levels of compliance with limits, looking across companies' own sites and those of their suppliers.

More sites regularly monitored for compliance, but a long way still to go

There are 1,057 sites in scope, consisting of 187 of the companies' own sites (based on data from 15 companies) and 807 supplier sites (based on data from 12 companies).* The majority of sites are reported to be subject to discharge limits. However, less than a third of all sites are reported as quantifying discharge levels to determine compliance with limits, while 13% are reported as compliant with the limits set.

Focusing in on suppliers' sites, the 'compliance gap' or 'data gap' becomes clear. Whereas 97 out of the pharma companies' 187 directly-operated sites included in this analysis are reported as compliant (52%), just 45 of the 870 suppliers' sites are reported as compliant (5.2%).

The challenge of compliance

Companies can have over 20 manufacturing sites and 200 suppliers' sites, making it a complex and time-consuming challenge to assess standards at all sites. Reaching compliance is a work in progress, which makes it key for companies to have environmental standards rooted in their long-term strategies, and to assign sufficient resources.

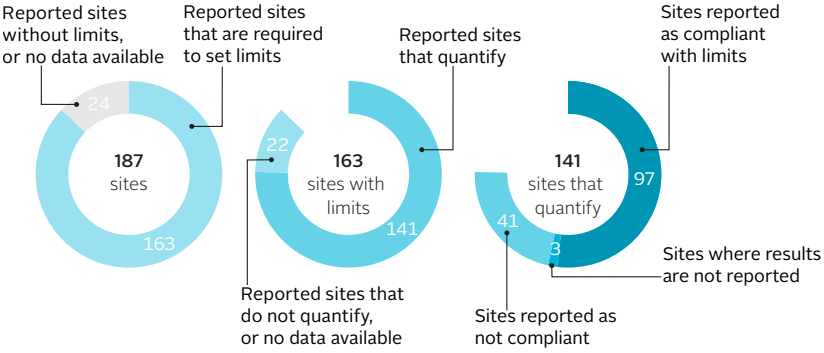
Data and transparency

This Benchmark captures data companies' practices at manufacturing sites along their supply chains. In future assessments, it will be important to take a step further and require companies to report on actual volumes of antibacterials that are manufactured per site to better map the risk of selection for resistance associated with manufacturing.

FIGURE 34. **Even where limits are set, quantification and compliance lags behind**

Companies' own manufacturing sites

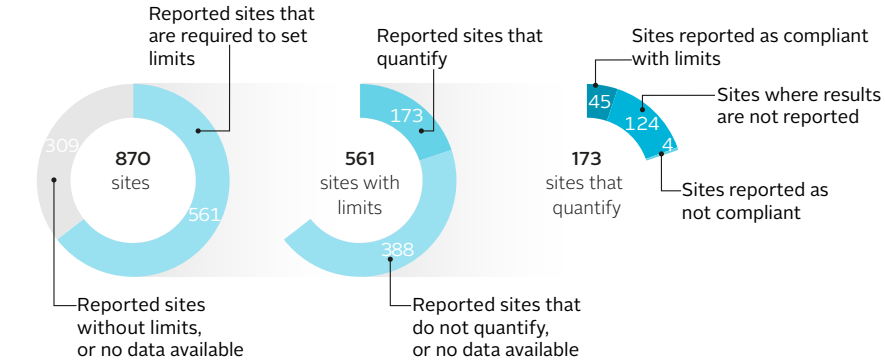
This figure shows how many of the pharma companies' 187 directly-operated manufacturing sites report setting or requiring limits, quantifying discharge levels and being compliant with set limits.



Discharge limits are set at 163 of the companies' own manufacturing sites – and of those sites, more than three quarters are reported as quantifying discharge levels. More than half are reported as compliant with discharge limits.

Suppliers' manufacturing sites

This figure shows how many sites, out of the total of 870 suppliers' sites, report setting or requiring limits, quantifying discharge levels and being compliant with set limits.



While 561 supplier sites are required to set discharge limits, quantification of discharge levels is only reported at 173 sites. That leaves 388 sites where, although limits have been set, no actions are reported as being taken to check whether the actual levels of antibacterial residue in wastewaters are compliant with these levels. Only 45 sites are reported as compliant with limits.
While four sites are reported as not compliant, compliance data is not available – or has not been made available – for the majority of suppliers' sites. It is crucial that pharma companies collect and report on compliance data across their entire supply chains.

* No data on any manufacturing sites is available for two companies: Alkem and MSD. No data on suppliers' sites is available for five companies: Fresenius Kabi, Hainan Hailing and Sun Pharma.

FIGURE 35. **Most sites are operated by third-party suppliers, and compliance rates here are low**
This figure shows how many sites (left) and what percentage of sites (right) are compliant with discharge limits, broken down by whether they are operated by large-research-based companies, generic medicine manufacturers, or third-party suppliers of both.

TABLE 7. **Supplier data often not available, but more positive signs at companies' own sites**
This table shows the percentage of each company's manufacturing sites, broken down by own and suppliers' sites, which are reported as compliant with discharge limits. Some company names are covered by NDAs. Many companies do not assess or report whether manufacturing sites are compliant with discharge limits.

Aurobindo reports that all of its 15 sites are compliant with discharge limits, making up almost half of the total number of generic medicine manufacturers' sites which are reported as compliant.

Of the 45 supplier sites reported as compliant, almost all of them were reported as such by GSK.

Level of compliance with discharge limits	At own sites	At suppliers' sites
High: 70-100%	**Number of companies: 5** • Aurobindo • GSK • Shionogi • Viatris • 1 large research-based company	**Number of companies: 1** • GSK
Medium: 40-70%	**Number of companies: 3** • 2 large research-based companies • 1 generic medicine manufacturer	**Number of companies: 0**
Low: 1-40%	**Number of companies: 2** • Cipla • Teva	**Number of companies: 2** • Shionogi • 1 large research-based company
No data	**Number of companies: 7** • 3 large research-based companies • 4 generic medicine manufacturers	**Number of companies: 14** • 5 large research-based companies • 9 generic medicine manufacturers

GOOD PRACTICE

GSK

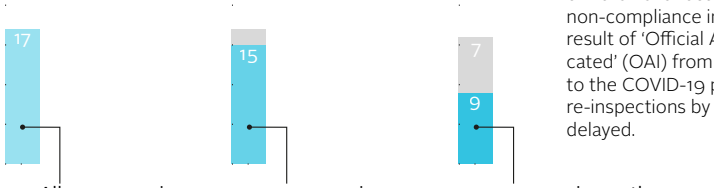
GSK reports that all 20 of its own sites and 37 out of 39 of its suppliers' sites are compliant with discharge limits set in the receiving environment. For its own manufacturing sites, GSK states that the most important steps to achieve compliance involve:

1. Optimising source control and cleaning procedures to reduce losses in wastewater. This includes vacuum cleaning and pre-rinsing of manufacturing equipment. Concentrated streams are collected at the point of generation and sent for proper disposal, such as incineration.
2. Installing pre-treatment technology such as pH or thermal hydrolysis, thin-film evaporation dryers, electrochemical oxidation, and multi-effect evaporation.

GSK reports that contracts with suppliers are discontinued when suppliers are not compliant with discharge limits. To assist suppliers towards reaching compliance, GSK promotes the use of tools and guidelines that help to assess and reduce their antibacterial discharges. Furthermore, GSK provides detailed guidance to suppliers based on experiences from the company's own manufacturing sites.

FIGURE 36. **Companies ensuring quality management systems across their supply chains**
Companies are expected to produce their antibacterials using the highest standards to ensure quality and minimise the risk that patients are exposed to sub-therapeutic levels, which drive AMR.[22]
While all companies have quality management systems (QMS) in place, several companies are also pushing up standards upstream.

During the period of analysis,** antibacterial sites operated by Aurobindo and a subsidiary of Teva have received a GMP non-compliance inspection result of 'Official Action Indicated' (OAI) from the FDA. Due to the COVID-19 pandemic, re-inspections by the FDA are delayed.



All 17 companies have a QMS at their own manufacturing sites

15 companies go further by auditing their suppliers' QMS

9 companies go the furthest by also requiring that suppliers audit their own suppliers' QMS*

* Otsuka reports that its suppliers do not have any suppliers of their own.
** The period of analysis is 22 June 2019 - 30 April 2021, inclusive.

RESPONSIBLE MANUFACTURING – TRANSPARENCY

Transparency from companies inches forward

Data on compliance with environmental standards at manufacturing sites can often only be reported by the Benchmark in an aggregate manner due to requests for confidentiality. Very few companies publicly report any level of detail on either the number of manufacturing sites audited, or on how many of these sites report compliance with safe levels. No company publicly reports on the actual levels of antibacterial residue entering local soil and water, and no company publishes its audit results.

The AMR Industry Alliance has a central role in setting strategy and deciding on public disclosure across the industry. But of the 12 members in scope, two companies (Fresenius Kabi and Otsuka) have not yet set limits at their own sites, and five companies (Aurobindo, Fresenius Kabi, Otsuka and Teva) have not yet formally required their suppliers to set limits. Cipla and Abbott report following the AMR Industry Alliance's guidelines, despite not being a member.

Two companies, GSK and Shionogi, stand out by reporting on whether the levels of antibacterial discharge found at their manufacturing sites (both directly-operated and suppliers' sites) comply with the limits set. This information is available in their annual or environmental reports. Novartis also reports on whether its own sites are compliant with pharmaceutical limits, though the company's data is not specific to sites producing antibacterials.

Of the 12 companies that report setting limits, nine also publish their commitment to these limits via their websites or annual reports. The three that do not are Abbott, Aurobindo and Cipla. Publicly committing to set limits is important so companies can be held accountable when not living up to their own words.

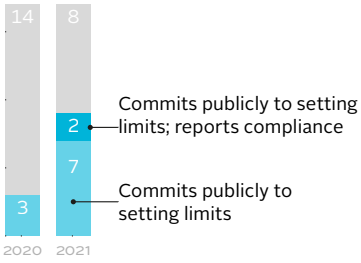
The benefits of transparancy

Without this information, it is difficult for independent third parties, including academic experts and government institutions, to critically assess if there is any progress and impact in making sure that antibacterial discharge levels are safe. A lack of transparency also hinders evaluation of the accuracy of mass balance estimations compared to sampling, and what dilution factors are applied.

The publication of both a) the methods used by the companies, and b) the resulting data, would permit deeper understanding of the current situation, opportunities for optimisation, and the dissemination of good practice. It would allow procurers to examine AMR-associated risks of a company's manufacturing practices in their procurement processes.[23]

FIGURE 37. **Number of companies which report setting limits at their own directly-operated manufacturing sites**

This figure shows how many of the 17 companies in scope publicly commit to setting limits and publishing compliance with limits for their own sites. More companies now make this commitment compared to the 2020 Benchmark.



SHIONOGI

Environmental report 2020

Shionogi leads the way when it comes to public disclosure, by publishing many aspects of its environmental risk-management strategy in its environmental report. The company shares which antibacterials it has in its portfolio, and maps the manufacturing of these products to the company's own sites and suppliers' sites, reporting which are compliant with discharge limits. Furthermore, the location of suppliers and the name of its only external waste-treatment plant are also disclosed. Altogether, Shionogi serves as a positive example of a company that provides clarity about its antibacterial manufacturing supply chain.

RESPONSIBLE MANUFACTURING – ANTIFUNGALS

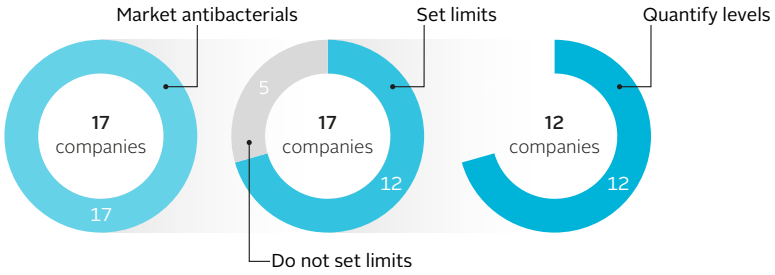
Companies do not prioritise antifungals in environmental risk management

As in 2018 and 2020, this Research Area focuses on antibacterials. However, antifungals are an area of emerging concern due to the high rate of cross-resistance between compounds employed as both broad-spectrum human antifungals and fungicides in agriculture.[24] The WHO is concerned about the public health threat of fungal infections, together with the rise in antifungal resistance, and is therefore developing a global fungal priority pathogens list to make sure R&D efforts are effectively prioritised.[25]

The list published by the AMR Industry Alliance includes targets for discharge limits for antifungals. However, in recent years, targets for 21 antifungal products in scope, marketed by 11 companies, have been removed from their list.[19] As a result, only 13 out of all 120 (11%) antifungal products in scope have a defined PNEC value which sets out what concentration would be considered safe. While the Alliance is steering away from antifungals, it is important that companies ensure limits apply to all antifungal products they manufacture and bring to market. The scientific field also has a role to play in defining science-based targets for more antifungals.

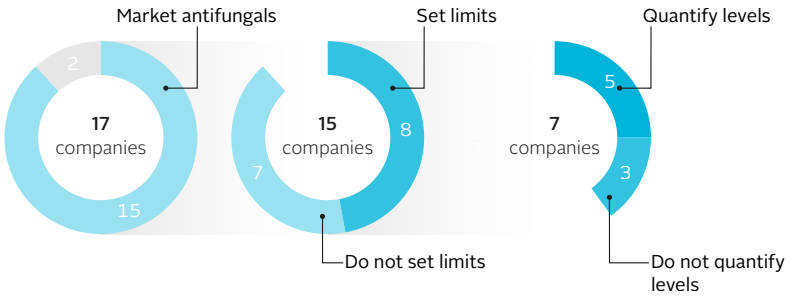
FIGURE 38. **How do the companies' approaches to environmental risk management differ between antibacterial and antifungal products?**

Antibacterials



All 17 companies in scope are marketing antibacterial products. The majority of companies report that they set limits, and that they quantify levels to check whether limits have been met.

Antifungals



Fifteen of the 17 companies in scope are marketing antifungal medicines. Just over half report that they set limits, and only a third report that they quantify discharge levels to assess whether limits are met.

Eight companies report an environmental strategy that covers antifungal manufacturing compared to seven in 2020, showing little progress.

RESPONSIBLE MANUFACTURING

Looking ahead

There are many actions which companies, governments, scientists, procurers and investors can take to break the link between antibacterial manufacturing and antimicrobial resistance, by ensuring that unsafe quantities of antibacterials are not discharged into the environment. This page sets out the positive actions each group of stakeholders can take.

COMPANIES

Increase transparency, e.g. via the AMR Industry Alliance, about the actual levels of antibacterial residue entering the environment. This would allow other stakeholders such as academics, procurers and government institutions to study the relationship between wastewater management and AMR, as well as independently assess companies' performance and progress.

At companies' own sites

- Follow through on progress in setting limits by ensuring full compliance with those limits.
- Apply limits directly to wastewater, instead of applying limits in receiving environments such as rivers.

At suppliers' sites

- Ensure all sites monitor discharge levels to assess compliance with limits, and report on the results.
- Share knowledge and experience from directly-managed sites, in order to help suppliers manage their own wastewater disposal.

At waste treatment plants

- Extend environmental risk management strategies to waste treatment plants, to assure responsible processing of industrial waste streams with high concentrations of antibacterials.
- Share data on water flows, for accurate quantification of discharge levels.

SCIENTIFIC FIELD

- Expand the evidence base and refine the definition of safe limits for a wider range of antibacterials and antifungals.
- Further increase the broader understanding of the role of environmental bacteria, wastewaters and selection pressures in the development of AMR.

GOVERNMENTS AND PROCURERS

- Develop regulatory frameworks, as current environmental regulations do not include limits on the levels of antibacterials allowed in wastewaters from manufacturing.
- Include environmental regulations and transparency stipulations in procurement contracts for products subsidised with public funding, in order to promote responsible behaviour.
- Require public disclosure from companies, not just on discharge levels but also on their supply chains. For example, the New Zealand Medicines and Medical Devices Safety Authority collates and publishes information from companies on the full supply chain of each marketed product in a publicly available database.[26] Such information includes: 1) where and by who the products are manufactured, packaged, and released; 2) which suppliers (including names and locations) supply each active ingredient; 3) the product sponsors.
- Spur public-private collaborations with a focus on removing antibacterials from industrial wastewater. For example, the Responsible Antibiotics Manufacturing Platform (RAMP) works with multiple stakeholders towards more sustainably-produced antibiotics and transparency.[27] Another international collaboration aims to develop a system for characterising the environmental risks of existing APIs. Such a system could also be used by companies to identify environmental concerns related to AMR earlier in the drug development process.[28] Finally, a Dutch consortium aims to develop technological solutions and innovation capacity to reduce antibacterial waste streams.[29]
- Use sustainability-focused policies to stimulate companies to meet environmental criteria. Companies are then incentivised to gain a competitive advantage to secure tenders or sales contracts, as applicable.[31,32] This approach has been piloted in Sweden and Norway.[32,33]

INVESTORS

- When making investment decisions, consider whether companies manufacture in a way that is environmentally responsible and mitigates the risk of AMR.
- Encourage companies to participate in sustainability-focused initiatives and pilot programmes.

REFERENCES

1. Changing Markets. Superbugs in the Supply Chain.; 2016.

2. Karkman A, Pärnänen K, Larsson DGJ. Fecal pollution can explain antibiotic resistance gene abundances in anthropogenically impacted environments. Nat Commun. 2019;10(1). doi:10.1038/s41467-018-07992-3

3. Kristiansson E, Fick J, Janzon A, et al. Pyrosequencing of antibiotic-contaminated river sediments reveals high levels of resistance and gene transfer elements. PLoS One. 2011;6(2). doi:10.1371/journal.pone.0017038

4. Li D, Yang M, Hu J, Ren L, Zhang Y, Li K. Determination and fate of oxytetracycline and related compounds in oxytetracycline production wastewater and the receiving river. Environ Toxicol Chem. 2008;27(1):80-86. doi:10.1897/07-080.1

5. Larsson DGJ. Pollution from drug manufacturing: Review and perspectives. Philos Trans R Soc B Biol Sci. 2014;369(1656). doi:10.1098/rstb.2013.0571

6. Bielen A, Šimatović A, Kosić-Vukšić J, et al. Negative environmental impacts of antibiotic-contaminated effluents from pharmaceutical industries. Water Res. 2017;126:79-87. doi:10.1016/j.watres.2017.09.019

7. Marathe NP, Shetty SA, Shouche YS, Larsson DGJ. Limited Bacterial Diversity within a Treatment Plant Receiving Antibiotic-Containing Waste from Bulk Drug Production. PLoS One. 2016;11(11):e0165914. doi:10.1371/JOURNAL.PONE.0165914

8. Marathe NP, Regina VR, Walujkar SA, et al. A Treatment Plant Receiving Waste Water from Multiple Bulk Drug Manufacturers Is a Reservoir for Highly Multi-Drug Resistant Integron-Bearing Bacteria. PLoS One. 2013;8(10):e77310. doi:10.1371/JOURNAL.PONE.0077310

9. Kraupner N, Hutinel M, Schumacher K, et al. Evidence for selection of multi-resistant E. coli by hospital effluent. Environ Int. 2021;150:106436. doi:10.1016/J.ENVINT.2021.106436

10. Johnning A, Moore ERB, Svensson-Stadler L, Shouche YS, Joakim Larsson DG, Kristiansson E. Acquired genetic mechanisms of a multiresistant bacterium isolated from a treatment plant receiving wastewater from antibiotic production. Appl Environ Microbiol. 2013;79(23):7256-7263. doi:10.1128/AEM.02141-13

11. Milaković M, Križanović S, Petrić I, et al. Characterization of macrolide resistance in bacteria isolated from macrolide-polluted and unpolluted river sediments and clinical sources in Croatia. Sci Total Environ. 2020;749. doi:10.1016/j.scitotenv.2020.142357

12. Larsson DGJ, Flach C-F. Antibiotic resistance in the environment. Nat Rev Microbiol 2021. Published online November 4, 2021:1-13. doi:10.1038/s41579-021-00649-x

13. Zieliński W, Korzeniewska E, Harnisz M, Drzymała J, Felis E, Bajkacz S. Wastewater treatment plants as a reservoir of integrase and antibiotic resistance genes – An epidemiological threat to workers and environment. Environ Int. 2021;156:106641. doi:10.1016/J.ENVINT.2021.106641

14. Osińska A, Korzeniewska E, Harnisz M, et al. Small-scale wastewater treatment plants as a source of the dissemination of antibiotic resistance genes in the aquatic environment. J Hazard Mater. 2020;381. doi:10.1016/j.jhazmat.2019.121221

15. Karkman A, Do TT, Walsh F, Virta MPJ. Antibiotic-Resistance Genes in Waste Water. Trends Microbiol. 2018;26(3):220-228. doi:10.1016/J.TIM.2017.09.005

16. Bengtsson-Palme J, Larsson DGJ. Concentrations of antibiotics predicted to select for resistant bacteria: Proposed limits for environmental regulation. Environ Int. 2016;86:140-149. doi:10.1016/J.ENVINT.2015.10.015

17. Tell J, Caldwell DJ, Häner A, et al. Science-based Targets for Antibiotics in Receiving Waters from Pharmaceutical Manufacturing Operations. Integr Environ Assess Manag. 2019;15(3):312-319. doi:10.1002/ieam.4141

18. Le Page G, Gunnarsson L, Snape J, Tyler CR. Integrating human and environmental health in antibiotic risk assessment: A critical analysis of protection goals, species sensitivity and antimicrobial resistance. Environ Int. 2017;109:155-169. doi:10.1016/j.envint.2017.09.013

19. AMR Industry Alliance. AMR Alliance Science-Based PNEC Targets for Risk Assessments. 2021;February:5.

20. AMR Industry Alliance. COMMON ANTIBIOTIC MANUFACTURING FRAMEWORK.; 2018. doi:10.1002/etc.3163/pdf

21. Ranade V V., Bhandari VM. Industrial Wastewater Treatment, Recycling and Reuse. Ind Wastewater Treat Recycl Reuse. Published online July 21, 2014:1-560. doi:10.1016/C2012-0-06975-X

22. Weinstein ZB, Zaman MH. Evolution of Rifampin Resistance in Escherichia coli and Mycobacterium smegmatis Due to Substandard Drugs. Antimicrob Agents Chemother. 2018;63(1). doi:10.1128/AAC.01243-18

23. Larsson DGJ, Fick J. Transparency throughout the production chain—a way to reduce pollution from the manufacturing of pharmaceuticals? Regul Toxicol Pharmacol. 2009;53(3):161-163. doi:10.1016/j.yrtph.2009.01.008

24. Verweij PE, Chowdhary A, Melchers WJG, Meis JF. Azole Resistance in Aspergillus fumigatus: Can We Retain the Clinical Use of Mold-Active Antifungal Azoles? Clin Infect Dis. 2016;62(3):362-368. doi:10.1093/cid/civ885

25. WHO Report. First meeting of the WHO antifungal expert group on identifying priority fungal pathogens. World Health Organization (WHO). Published 2020. Accessed September 5, 2021. https://www.who.int/publications/i/item/9789240006355

26. MEDSAFE: New Zealand Medicines and Medical Devices Safety Authority. Accessed October 20, 2021. https://www.medsafe.govt.nz/regulatory/DbSearch.asp

27. Responsible antibiotics manufacturing platform (RAMP) - SIWI. Accessed October 27, 2021. https://siwi.org/amr-ramp/?accordion-our-impact

28. IMI-PREMIER– Prioritisation and Risk Evaluation of Medicines in the EnviRonment. Accessed October 20, 2021. https://imi-premier.eu/

29. Dutch Consortium Antibiotics and, Pharmaceutical Residues from Water. Removal of Antibiotics and Pharmaceutical Residues in Water Urgent.; 2021.

30. Årdal C, Baraldi E, Beyer P, et al. Supply chain transparency and the availability of essential medicines. Bull World Health Organ. 2021;99(4):319. doi:10.2471/BLT.20.267724

31. SIWI. Reducing Emissions from Antibiotic Production . Published online 2020. Accessed October 20, 2021. www.siwi.org/publications

32. Regeringskansliet. Försöksverksamhet för miljöpremie i läkemedelsförmånssystemet. Published 2021. Accessed October 27, 2021. https://www.regeringen.se/pressmeddelanden/2021/05/forsoksverksamhet-for-miljopremie-i-lakemedelsformanssystemet/

33. New environmental criteria for the procurement of pharmaceuticals - Sykehusinnkjøp. Accessed November 8, 2021. https://sykehusinnkjop.no/nyheter/new-environmental-criteria-for-the-procurement-of-pharmaceuticals

CONTEXT

Appropriate Access

The antibiotics and antifungals available today make it possible to prevent and control the spread of infection in communities and hospitals. They cut the risk of infection after surgery, and protect people undergoing aggressive treatments, such as for cancer. Yet eight times as many people currently die from lack of access to medicine as from drug-resistant infections.[1] Action to improve the availability and accessibility of medicines and vaccines is urgently needed, with each antibiotic and antifungal being used responsibly to ensure it stays effective for as long as possible.

More people die from treatable infectious diseases than from drug resistance
An estimated 700,000 people die each year due to drug-resistant infections. By comparison, 5.7 million people die from treatable infectious diseases.[1] Most of these people live in low- and middle-income countries (LMICs).

Lack of access to medicine can drive up drug resistance
Shortages, stockouts and unavailability of medications can lead to patients being given ineffective or inappropriate drugs for their illnesses, contributing to AMR and giving pathogens extra opportunities to develop resistance.[2]

Pharma companies can improve access in LMICs
The range of actions which pharma companies can take includes registering medicines and vaccines for sale in a country, taking steps to address affordability and availability, building up the technical skills and knowledge needed for local manufacturing, and strengthening supply chains to prevent shortages.

HOW PHARMA COMPANIES CAN DIRECTLY ADDRESS ACCESS

Registration
Filing a product with national regulatory authorities in each country is a key step towards making it available. To expand access, companies should submit registration dossiers to LMIC authorities as rapidly as possible after first market launch.

Ensuring affordability
Globally, medicine is the largest household expenditure after food. In LMICs, up to 75% of health spending comes from people's own pockets.[1] Companies can make medicines and vaccines more affordable through equitable pricing, voluntary licensing agreements, and product donations.

Capacity building
Companies can contribute to local manufacturing capacity by helping LMIC-based companies build up their manufacturing knowledge and expertise, for example through technology transfers and voluntary licenses.

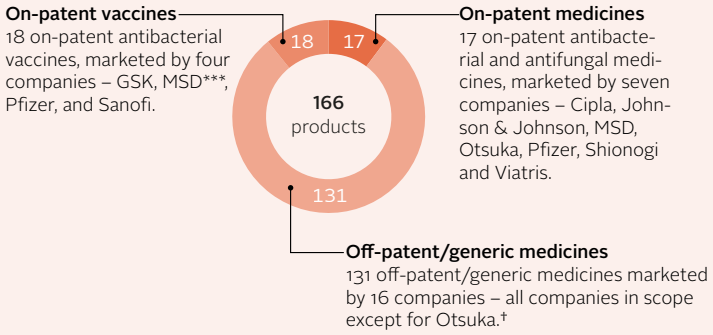
Preventing shortages
A continuous supply of good quality medicines, used responsibly, saves lives and reduces the risk from resistance. Companies can mitigate the risk of shortages in a range of ways, such as maintaining buffer stock, building resilient supply chains, and by predicting and aligning levels of supply and demand.

17 companies in scope for Appropriate Access

The 2021 AMR Benchmark examines the policies and practices of eight large research-based companies and nine generic medicine manufacturers, looking at their actions to ensure appropriate access to their medicines and vaccines. By volume and value of sales, these companies are among today's largest players in the global market for antibacterial and antifungal medicines, and therefore have significant capacity to improve access to their products in the countries with the highest need.[3]

FIGURE 39. **166 products in scope for this analysis**

Across the 17 companies, the Benchmark identified 166 products, which can be divided into three categories.



Companies in scope for the 2021 Benchmark

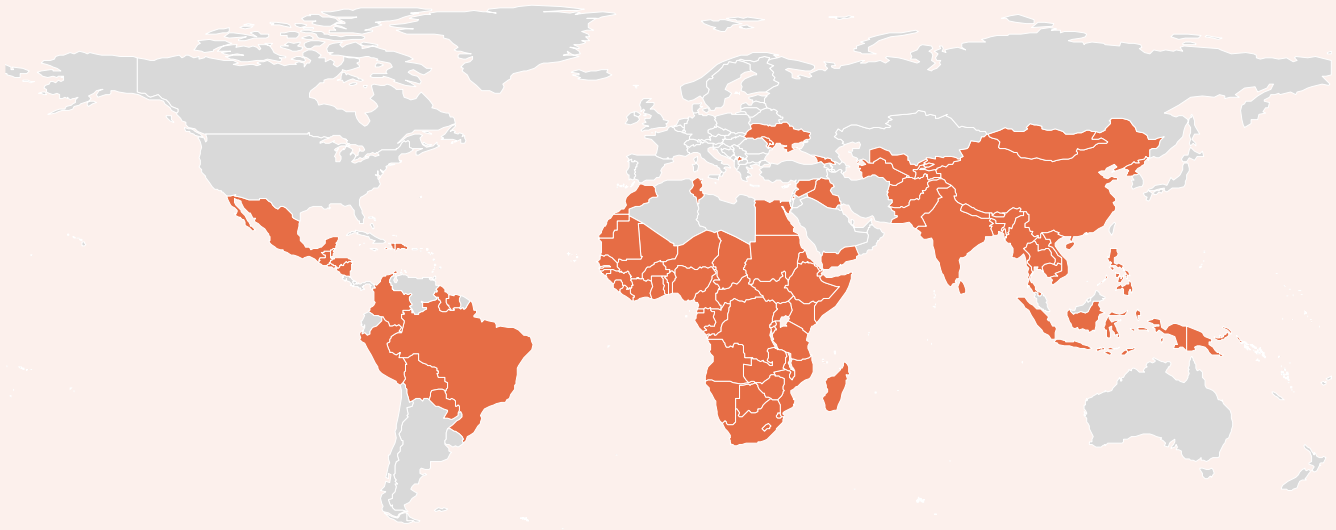
Together these companies account for 29,031.60 SU* million doses sold annually

	Large research-based companies	Country HQ
1	GlaxoSmithKline plc	GBR
2	Johnson & Johnson	USA
3	Merck & Co, Inc	USA
4	Novartis AG	CHE
5	Otsuka Pharmaceutical Co, Ltd	JPN
6	Pfizer Inc	USA
7	Sanofi	FRA
8	Shionogi & Co, Ltd	JPN

	Generic medicine manufacturers	
1	Abbott Laboratories	USA
2	Alkem Laboratories Ltd	IND
3	Aurobindo Pharma Ltd	IND
4	Cipla Ltd	IND
5	Fresenius Kabi AG	DEU
6	Hainan Hailing Chemipharma Corp Ltd	CHN
7	Viatris**	GBR
8	Sun Pharmaceutical Industries Ltd	IND
9	Teva Pharmaceutical Industries Ltd	ISR

FIGURE 40. **102 countries in scope for access metrics in this analysis**

This map shows the 102 low- and middle-income countries in scope of the Benchmark for this Research Area. These are countries where resistance rates are highest, and where people face the highest burdens of disease.



* Source: IQVIA Midas 2017 anti-infectives data. Companies with sales volumes below 1.000 SU million are not included in this number.

** Mylan has been renamed Viatris, following closing of merger with Upjohn, a division of Pfizer, in 2020.
*** Merck & Co, Inc (Kenilworth, NJ, United States)

† Only the top two off-patent/generic medicines by global sales volume within each Appropriate Access category (AWaRe antibiotics, off-patent TB medicines and antifungals) were selected for analysis.

APPROPRIATE ACCESS – REGISTRATION

Slow progress on registering products in poorer countries

Filing for registration is a vital first step towards introducing a medical product into a country, as successful registration means that a product is now allowed to be imported and sold. Companies can register their products with the national regulatory authorities of each country, by filing dossiers of technical, medical, and scientific information. Alternatively, in some cases they can make use of special import processes that can waive registration for certain essential medicines, such as tuberculosis medicines.

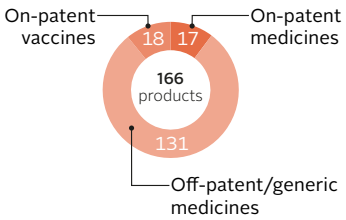
Typically, pharmaceutical companies first file for registration in higher-income countries with larger markets. However, considering that less wealthy countries often have the highest need for new products, pharmaceutical companies should register their products widely in low- and middle-income countries (LMICs).

FIGURE 41. **The data set for this analysis**

Products: 166

Companies: 17

Countries: 102



Some signs of progress, much further to go

As in the 2020 AMR Benchmark, in 2021 the products in this analysis are generally not widely filed for registration across the 102 LMICs in scope.

Only six on-patent medicines have been filed in ten or more of these countries. Vaccines are filed much more widely than patented medicines, reflecting high international demand as well as the impact of supranational pooled procurement agencies such as Gavi, The Vaccine Alliance.

CHALLENGES

Company decision-making

There are various reasons why a company may or may not file a product for registration in a specific country, including:

- Competing products already on the market in that country;
- Market size and financial opportunities;
- Policies on pricing transparency;
- Political instability, conflict, or economic sanctions;
- Unclear local regulatory requirements, and long processing times for registration.

Working with regulators

An increasing number of LMICs now require marketing authorisation to license and manufacture a product. Yet, the submission of dossiers can be lengthy and burdensome for companies. Some regulatory authorities may also lack the technical expertise to assess the dossier, resulting in long waiting times before regulatory approval.

Lack of transparency

Few online regulatory databases yet track the registration of medicines in smaller LMICs. Because regulatory agencies in these countries may lack the capacity for building and updating such databases, companies can play a role in being more transparent on where they file their medicines for registration. For example, Johnson & Johnson is the only company in scope to publicly disclose where it filed its MDR-TB medicine bedaquiline (Sirturo®) for registration.[4]

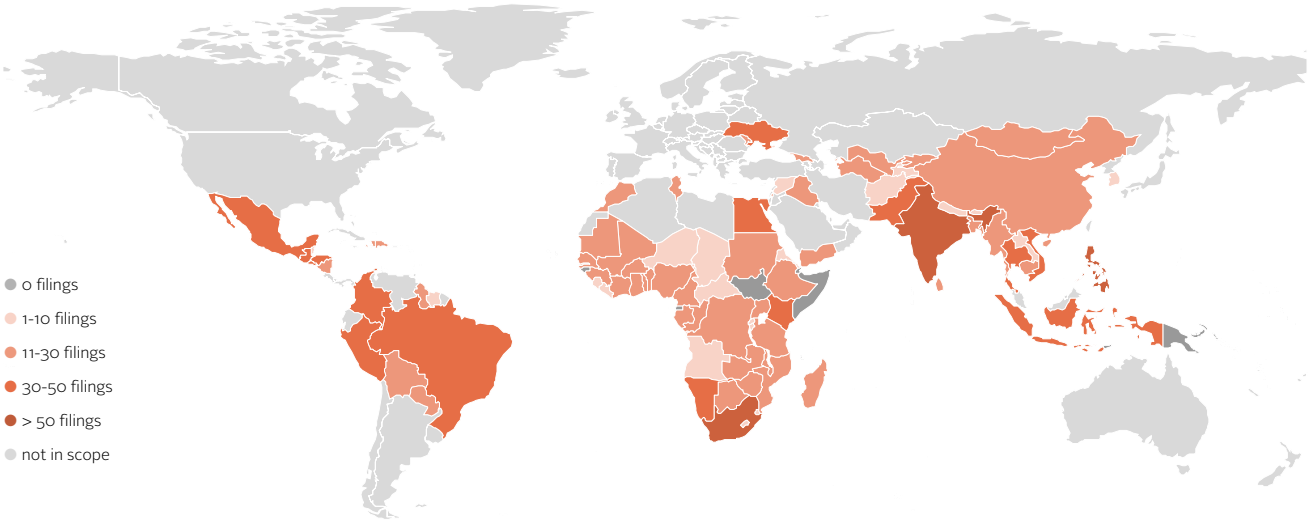
Overcoming access challenges

In response to some of these challenges, a number of bodies and programmes have been established, and are already providing companies with support for product registration:

- The WHO Collaborative Registration Procedure
- The African Medicines Regulatory Harmonization (AMRH) programme
- The African Medicines Agency (AMA)

FIGURE 42. **Which LMICs have the most products being filed?**

This map highlights the number of the 166 products in scope which have been filed for registration in each of the 102 LMICs included in this analysis.



Which LMICs account for the least registration filings?

There are 14 countries in which none of the products in scope are known to have been registered. These countries include Somalia and South Sudan, which face political instability, as well as small countries like Tuvalu and Vanuatu, which are hard-to-reach countries that rely on imports for most of their medicines.

Which LMICs account for the most registration filings?

The five countries within the scope of this analysis where the most registrations have been registered are South Africa, the Philippines, India, Brazil, and Thailand. More than 45 filings were reported in those countries during the period of analysis, with South Africa benefitting from the highest number of filings (56 in total, across the 166 products).

Compared to other LMICs, these countries provide greater revenue opportunities for pharma companies due to their large patient populations in need, as well as mixed payments from private insurances, public health systems or out-of-pocket expenditure.

Many on-patent medicines are not widely filed for registration

On-patent antibiotics and antifungals are typically indicated for very specific cases or complicated infections, and are targeted at smaller patient populations. Due to their more restricted use, companies have a lower expectation that they will gain a high return on investment, and can find it difficult to estimate the number of people who could benefit from those medicines in LMICs.

Although volume expectations are lower than for high-volume generic medicines or vaccines, companies need to continue to register their patented antibiotics and antifungals, especially those which do not benefit from pooled procurement mechanisms, as this is the first step in providing long-term access for patients in low- and middle-income countries.

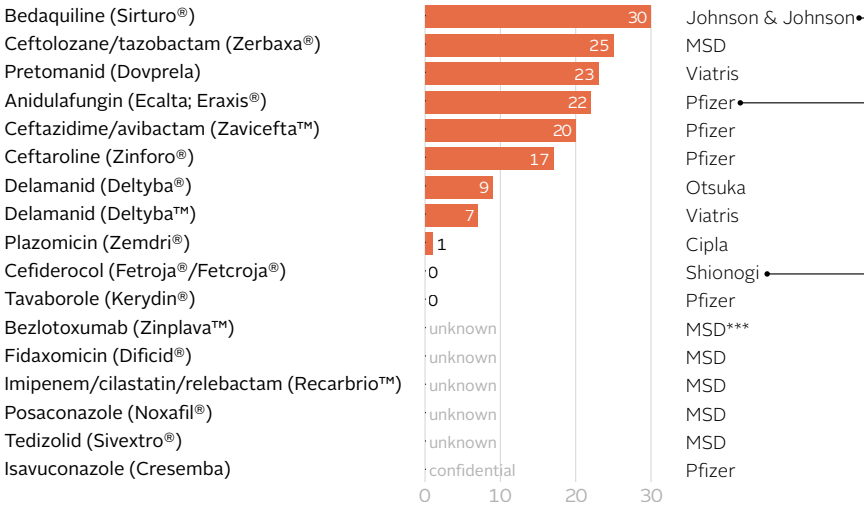
Only three companies – Johnson & Johnson, Pfizer and Viatris – have registered any of their patented medicines in the 34 countries defined as 'low-income countries'.

- MDR-TB* medicine bedaquiline (Sirturo®) is approved in seven low-income countries (Democratic Republic of Congo, Burundi, Ethiopia, Rwanda, Tanzania, Uganda and Zimbabwe).
- Ceftazidime/avibactam (Zavicefta™), used to treat complicated intra-abdominal infections, complicated urinary tract infections (cUTIs) and hospital-acquired pneumonia, is approved in three low-income countries (Ethiopia, Tanzania, and Uganda).
- M/XDR-TB** medicine pretomanid has been filed for registration in five low-income countries (Democratic Republic of Congo, Ethiopia, Mozambique, Tajikistan and Zimbabwe).

While Johnson & Johnson and Viatris have filed their TB medicines in countries with a high TB burden, Pfizer reports that it has filed Zavicefta™ in these countries based on local patient and provider needs.

FIGURE 43. **Which on-patent medicines are filed most widely?**

This figure shows in how many of the 102 countries each on-patent medicine is filed for registration.



Johnson & Johnson's MDR-TB medicine, bedaquiline, has been filed for registration in 30 of the LMICs in scope, and is also available via the GDF-Stop TB Partnership in almost all of the countries in scope. The second most widely-filed medicine is MSD's ceftolozane/tazobactam (Zerbaxa®), used to treat complicated urinary tract and intra-abdominal infections.

Pfizer's anidulafungin (Ecalta®), for treatment of invasive candidiasis, is the most widely-filed antifungal.

Shionogi's on-patent antibiotic cefiderocol (Fetroja®/Fetcroja®), used to treat infections caused by aerobic Gram-negative bacteria when there are few treatment options available, was first approved by the FDA in 2019 and has not yet been filed for registration in low- and middle-income countries. Cefiderocol was newly included in the WHO 22nd Model List of Essential Medicines (EML) in 2021 as a 'Reserve group' antibiotic. In July 2021, Shionogi, the Global Antibiotic Research and Development Partnership (GARDP) and Clinton Health Access Initiative (CHAI) announced a memorandum of understanding (MOU) to accelerate access to cefiderocol in low- and middle-income countries.

* Multidrug-resistant tuberculosis
** Multidrug- and extensively drug-resistant tuberculosis
*** MSD declined to provide information about these products to the Benchmark. Information about where products are registered is used by governments, NGOs and others to inform procurement decisions. Generic medicine manufacturers also use such information to inform decisions about where to expand their business operations.

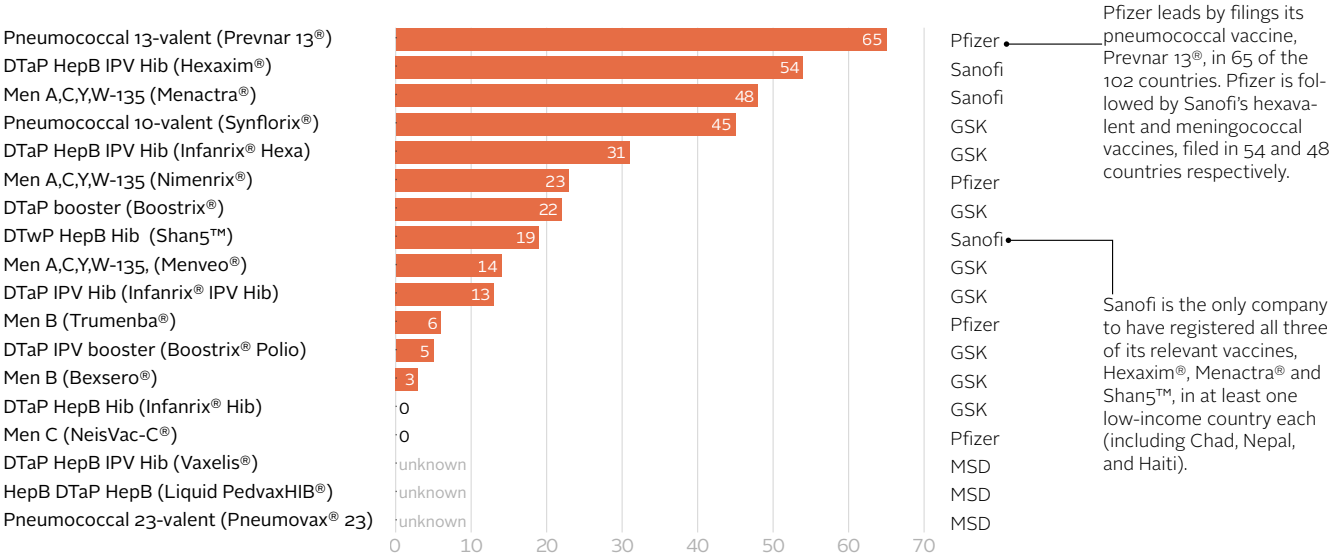
As a group, vaccines are more widely filed than medicines

Vaccines have a major role to play in curbing AMR, because they can decrease the number of cases of infectious diseases, and thus decrease antibiotic use. This slows down the emergence and spread of AMR.[5]

Vaccines are more likely than medicines to be filed in a broad range of countries, in part because many of them have been on the market for longer than on-patent medicines. Vaccines can also represent a secure long-term financial opportunity for companies, because they cover broad populations (e.g. through national immunisation programmes) and can benefit from pooled procurement mechanisms such as Gavi, The Vaccine Alliance. Pharma companies can also benefit from long-term patent protection for vaccines; some of the vaccines considered in this analysis were first approved more than 20 years ago.

FIGURE 44. **Which on-patent vaccines are filed most widely?**

This figure shows in how many of the 102 countries each on-patent vaccine is filed for registration.



Pfizer leads by filings its pneumococcal vaccine, Prevnar 13®, in 65 of the 102 countries. Pfizer is followed by Sanofi's hexavalent and meningococcal vaccines, filed in 54 and 48 countries respectively.

Sanofi is the only company to have registered all three of its relevant vaccines, Hexaxim®, Menactra® and Shan5™, in at least one low-income country each (including Chad, Nepal, and Haiti).

DTaP=Diphtheria, Tetanus, acellular Pertussis
DTwP=Diphtheria, Tetanus, whole-cell-pertussis
HepB=Hepatitis B
IPV=inactivated Poliovirus
Hib=Haemophilus influenzae type b
Men A,C,Y,W-135=Meningococcal serogroups A, C, Y, W-135
Men B=Meningococcal serogroup B
Men C=Meningococcal serogroup C

Which off-patent/generic products are filed most widely?

The Benchmark looks at the off-patent/generic medicines with the highest volume of sales. The number of registration filings varies greatly by access category. Access and watch antibiotics (defined according to the WHO's AWaRe classification) are filed for registration much more widely than reserve antibiotics (16 access countries on average), because they are more widely used and represent a higher sales volume for companies.

Reserve antibiotics are largely overlooked by pharmaceutical companies. Although they should only be used as an option of last resort and can thus represent fewer financial incentives for companies, reserve antibiotics are also essential for controlling some of the most resistant pathogens. Yet, they are filed in only two out of 102 access countries in scope on average.

Of the products in scope, only 39% of off-patent/generic medicines supplied by large research-based companies are filed in more than 10 access countries. For products in scope which are marketed by generic medicine manufacturers, that number drops down to 29% filed in more than 10 LMICs.

Methodology: products in this analysis

Within each access category, each company's top two off-patent products by sales volume were selected for analysis, using IMS global sales data.*

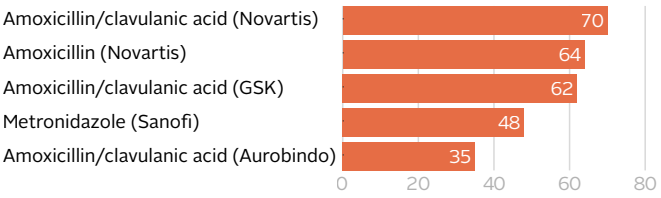
These categories are Access, Watch, Reserve (AWaRe), antifungals, and antituberculosis. However, off-patent/generic TB medicines were removed from the analysis because they did not meet current TB treatment guidelines.

FIGURE 45. **Which off-patent/generic products are filed most widely?**

Of the products in scope, these graphs show the five most widely filed off-patent/generic medicines targeting bacterial and fungal infections, broken down per the AWaRe classification, as well as antifungals.

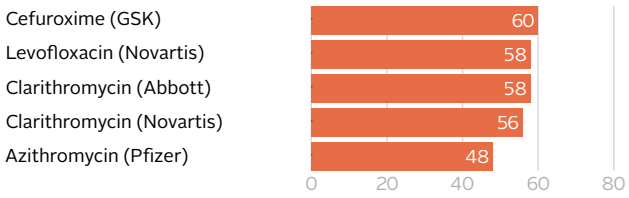
Access Group

'Access' antibiotics should be readily available, affordable and quality-assured. On average, the 'Access' antibiotics included in this analysis are filed in only 16 out of the 102 LMICs in scope.



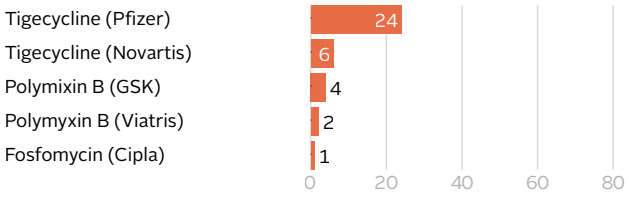
Watch Group

Second-line treatments that should be prescribed only for specific indications, since they are at higher risk of AMR. On average, the 'Watch' antibiotics included in this analysis are filed in only 16 out of the 102 LMICs in scope.



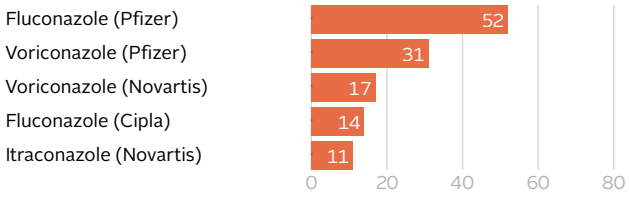
Reserve Group

Last resort or third-line treatments that should be used when all others fail, in order to limit the risk of resistance. On average, the 'Reserve' antibiotics included in this analysis are filed in just two of the 102 LMICs in scope. Although they should only be used as a last resort option, they are also essential for controlling some of the most resistant pathogens.



Antifungals

While these are not included as part of the WHO AWaRe Groups, they are necessary to treat fungal infections. On average, the antifungal products in this analysis are filed in nine out of the 102 LMICs in scope.



N.b., off-patent/generic products (such as older antibiotics like amoxicillin) are often produced and sold by multiple different companies, which means that the same product's INN (International Nonproprietary Name) can be registered several times.

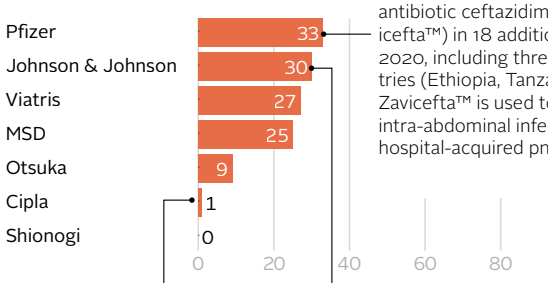
* Sales volumes specific to low- and middle-income countries are not reflected in global sales data.

How the companies compare in registering their on-patent products

The Benchmark looks at whether the companies are registering the patented products in their portfolios in the 102 LMICs in scope, and in how many of these countries they have filed for registration. The figures below show higher numbers of registrations for companies' on-patent vaccine portfolios than for on-patent medicines, with Pfizer performing strongly in both categories.

FIGURE 46. **Registration filings for on-patent medicines, by company**

There are 17 on-patent antibacterials and antifungals covered by this analysis, marketed by seven companies. This figure shows the number of countries in scope in which each company has registered at least one of its products.



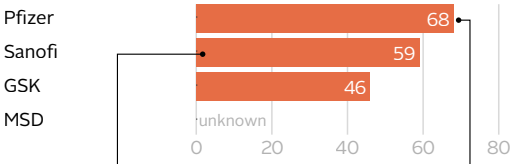
Pfizer's has five on-patent medicines in scope. Notably, Pfizer filed its reserve antibiotic ceftazidime/avibactam (Zavicefta™) in 18 additional countries since 2020, including three low-income countries (Ethiopia, Tanzania, and Uganda). Zavicefta™ is used to treat complicated intra-abdominal infections, cUTIs, and hospital-acquired pneumonia.

Generic medicine manufacturer Cipla registered its newly-acquired on-patent medicine plazomicin (Zemdri®) in India. This reserve antibiotic is used to treat complicated urinary tract infections.

Johnson & Johnson has only one eligible on-patent medicine, bedaquiline (Sirturo®), but has filed for registration in 30 countries.

FIGURE 47. **Registration filings for on-patent vaccines, by company**

There are 18 antibacterial vaccines covered by this analysis, marketed by four companies. This figure shows the number of countries in scope in which each company has registered at least one of its products.



Sanofi has registered at least one of its three on-patent vaccines (Hexaxim®, Menactra® and Shan5™) in 59 countries.

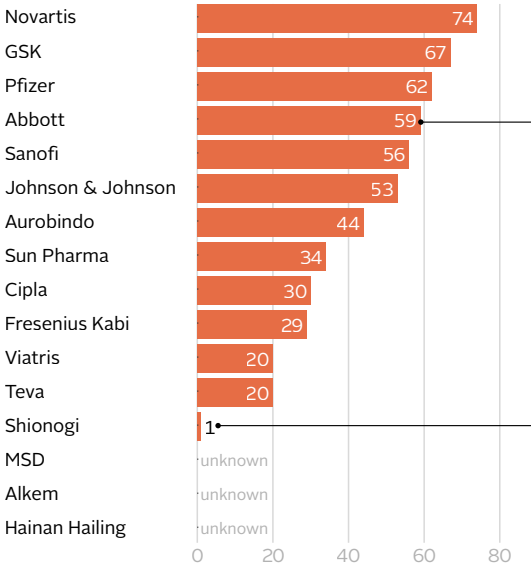
Four of Pfizer's on-patent vaccines target a disease in scope. Of these four, its most widely filed vaccine is the Pneumococcal Conjugate Vaccine (13-valent) Prevnar13®, which is filed in 65 LMICs.

How the companies compare in registering their off-patent/generic medicines

The generic medicine manufacturers in scope have larger portfolios of off-patent/generic medicines that qualify for analysis than the large research-based companies. However, looking at the products in scope, the large research-based companies file each of their off-patent medicines more widely (in 52 of the 102 LMICs, on average) compared to the generic medicine manufacturers (34 on average).

FIGURE 48. **Registration filings for off-patent/generic medicines, by company**

There are 131 off-patent/generic medicines covered by this analysis, marketed by 16 companies. This figure shows the number of countries in scope in which each company has registered at least one of its products.



Among the generic medicine manufacturers in scope, Abbott has filed its off-patent/generic medicines in the highest number of LMICs.

Shionogi's off-patent medicines, the antibiotics flomoxef and cefcapene, are only approved in China. These two medicines did not meet all regulatory requirements as their respective clinical trials were conducted prior to the ICH guidelines. Shionogi does not actively promote these medicines. However, in July 2021, GARDP identified flomoxef as a potential treatment option for neonatal sepsis.

GOOD PRACTICE

Viatris: TB medicine pretomanid

In 2020, Viatris newly filed its TB medicine pretomanid for registration in 23 of the LMICs in scope. Pretomanid was developed by the TB Alliance and is approved by the FDA and the EMA for the treatment of extensively drug resistant TB (XDR-TB), as well as for treatment-intolerant/non-responsive multi-drug resistant TB (MDR-TB), as part of a six-month 'BPaL' oral treatment regimen that combines bedaquiline, pretomanid, and linezolid. WHO recommendations for the use of pretomanid and the BPaL regimen currently apply only under operational research conditions. One of the countries where Viatris filed pretomanid for registration is India, a country with a high burden of TB. The company took this step less than one year after receiving its initial FDA approval, demonstrating a focus on filing for registration across a wider range of countries.

APPROPRIATE ACCESS – ACCESS STRATEGIES

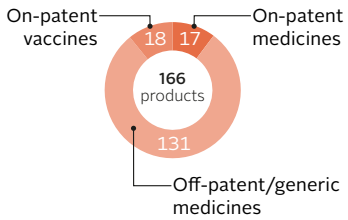
What are companies doing to expand access to antibiotics and antifungals in LMICs?

More than 80% of people alive today live in low- and middle-income countries (LMICs). They face some of the highest burdens of infectious diseases, and some of the highest rates of drug resistance, but often do not have access to the medicines and vaccines they need. Whether they can access these medicines and vaccines depends on several factors, including whether – and how – pharmaceutical companies work to make their medicines and vaccines more available, accessible, and affordable.

Across the 17 companies in scope, the Benchmark examined 166 antibacterial and antifungal medicines and vaccines. Looking at these products, the Benchmark considered companies' efforts to identify the greatest needs for their products, and any gaps in accessibility. Companies were assessed on how they set prices, both at country level and for different populations within each country. In addition to assessing pricing strategies such as tiered pricing and donations, the Benchmark considered other strategies to expand the accessibility of products. The Benchmark also looked for evidence of patient reach for each access strategy reported by the companies.

Strategies for vaccines vs medicines
When it comes to ensuring access to vaccines rather than medicines, different strategies are commonly used. Many vaccines are purchased in bulk by multilateral organisations on behalf of groups of buyers, usually national governments. The same 'pooled procurement' approach is often used for medicines for diseases such as HIV/AIDS, malaria and tuberculosis.

Products in scope for this analysis



KEY QUESTIONS

What types of access strategies are pharmaceutical companies using?
There are several types of access strategies. Three key strategies are: 1) pricing actions, such as not-for-profit pricing or price caps; 2) voluntary licensing, which can boost competition and supply; and 3) product donations.

Where are access strategies being put into action?
Strategies can be applied either locally, at the national level, or regionally. The Benchmark assesses whether countries with the highest need for better access are being targeted.

Are companies taking account of people's ability to pay?
Globally, medicine is the largest household expenditure after food. Healthcare costs can push families into bankruptcy. Companies can use a range of measures to assess the affordability of a specific price-point.

Are companies reporting how many patients their strategies are reaching?
Per access strategy, companies should prioritise populations with the biggest need, and monitor their success at reaching patients.

CONSIDERATIONS

Product and geographic coverage
Most of the access strategies reported focus on a small set of countries and products. Companies need to be more transparent with their strategies and cover a wider range of countries, people, and treatments. Local access initiatives are still driving access overall, and should be sustainable on the long-term.

Affordability
To address affordability more efficiently, companies should look at implementing price reductions or price segmentation (such as second brand approach, price caps or patient assistance programmes) in more countries, especially low-income countries.

Supranational procurement
Access strategies for supranationally procured products are generally better structured and applied more widely. Pentavalent and pneumococcal vaccines, as well as the TB medicines in scope, are procured through organisations including Gavi, The Vaccine Alliance and the GDF Stop-TB Partnership and distributed to a wide range of eligible countries.

Donations
Five companies report making donations of their antibacterial and antifungal medicines: GSK, Pfizer, Sanofi, Teva and Viatris. Product donations involve a few Access and Watch antibiotics or antifungals. Product donations continue to play an important role in eliminating, eradicating, or controlling some diseases that affect populations living in LMICs. For people living in poverty, donations may be their only chance of getting access to the treatment they need.

Many ways for companies to improve local availability, yet few are being used

There are a wide range of tools available to pharmaceutical companies to increase local availability of vital antimicrobials in poorer nations. With each medicine or vaccine, pharmaceutical companies should consider the full range of access strategies in the toolkit to work out what is most useful.

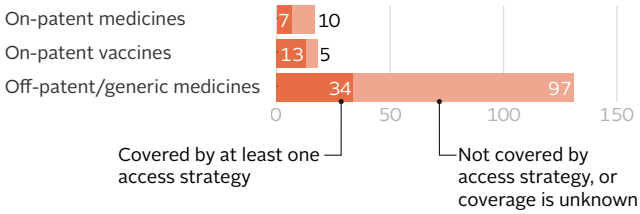
However, as identified in the 2018 and 2020 Benchmarks, companies are making minimal use of the many access strategies in the arsenal. This is the case both in terms of the proportion of products covered by access strategies, and in terms of the countries that are being targeted.

What is the 'gold standard' for access strategies?

Companies take a proactive approach and show willingness to reach more people with their medicines and vaccines in LMICs, including countries particularly affected by the relevant disease(s). Companies are using and combining a range of strategies. Access strategies are clear, well described, and detailed – specifying patient and geographic reach, and considering ability to pay where appropriate. Companies commit to long-term access plans.

FIGURE 49. **Number of products covered by at least one access strategy, broken down by category**

Of the 166 products examined by the Benchmark, 54 are covered by at least one access strategy. A wide range of strategies count towards this figure, including donations, patient assistance programmes, voluntary licensing, tiered and equitable pricing policies



Seven of 17 on-patent medicines in scope are covered by at least one access strategy. These seven products are marketed by five companies: Johnson & Johnson, MSD, Otsuka, Pfizer and Viatris.

Pharma companies use a range of access strategies, but not for many products

The 17 companies in scope report various access strategies which apply to their products. However, these are not comprehensively used.

In the case of on-patent medicines and vaccines, large research-based companies hold the key to access, and can unlock access by using strategies such as public/private partnerships, equitable and tiered pricing, voluntary licensing agreements, patient assistance programmes, or donations.

Both large research-based companies and generic medicine manufacturers can play an important role in maximising the availability of essential off-patent/generic medicines. They report doing so through competitive bidding, direct sales contracts, or through mandatory cost containment measures that apply to generic medicines in many countries.

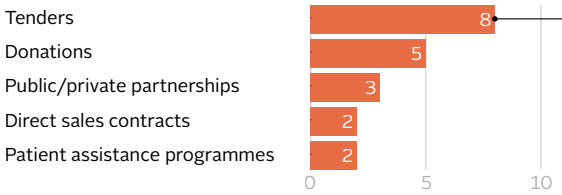
FIGURE 50. **Number and type of access strategies being used for on-patent medicines**

Of the seven companies with products in this analysis, five companies report using access strategies:* Johnson & Johnson, MSD, Otsuka, Pfizer, and Viatris. This graph shows the types of strategies being used to expand access to the 17 on-patent medicines.

Of the 18 reported access strategies for on-patent products, 12 involve tuberculosis medicines. Newer antibiotics and antifungals are covered by only six of these strategies. Unlike TB medicines, new antibiotics and antifungals are less likely to benefit from the support of pooled-procurement mechanisms, and rely mainly on companies actions to expand their access in LMICs.

FIGURE 51. **Number and type of access strategies being used for off-patent/generic medicines**

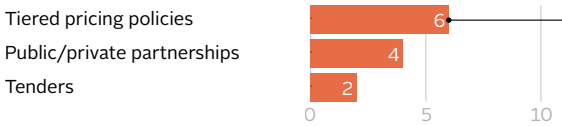
Of the 16 companies with products in this analysis, 13 companies report using access strategies: Abbott, Aurobindo, Cipla, Fresenius Kabi, GSK, Johnson & Johnson, MSD, Novartis, Pfizer, Sanofi, Sun Pharma, Teva and Viatris. This graph shows the type of strategies being used to expand access to the 131 off-patent/generic medicines.



Across the 16 companies supplying off-patent/generic medicines to low-and middle-income countries, three large-research based companies (including Novartis and Sanofi) and four generic manufacturers (Aurobindo, Cipla, Fresenius Kabi and Teva) report participating in tenders in the public or private sector.

FIGURE 52. **Number and type of access strategies being used for on-patent vaccines**

All of the four companies with products in this analysis – GSK, MSD, Pfizer and Sanofi – report using access strategies for these on-patent vaccines. This graph shows the type of strategies being used to expand access to their 18 on-patent vaccines.



All four companies report using tiered pricing policies. Tiered pricing policies tend to apply globally, with pricing tiers defined by countries' ability to pay.

* See appendix for definitions.

Do companies track how many people they reach with their access strategies?
The Benchmark looked for evidence of patient reach resulting from the access strategies employed by the companies.
Despite the strategies used, the burden of disease is still significant and not enough patients are reached. Many companies do not report the numbers, although companies are more likely to report their patient reach data for supranationally-procured medicines and vaccines, and for off-patent/generic medicines with high volumes of sales. Some medicines are still overlooked, such as the 23 off-patent reserve antibiotics in scope, for which no patient reach data was reported. However, some notable examples of patient reach can be provided for both on- and off-patent products.

EXAMPLES OF TRANSPARENCY ON PATIENT REACH

TB medicines distributed through the GDF-Stop TB Partnership
In 2020, at least 125,000 treatment courses of Johnson & Johnson's bedaquiline (Sirturo®) were ordered through the GDF-Stop TB Partnership, and at least 25,000 treatment courses of Otsuka's delamanid (Deltyba®) were distributed to more than 80 countries between 2016 and 2020. The GDF also supplied 400 treatment courses of pretomanid (Dovprela) to 10 countries in 2020.

GSK: off-patent/generic medicines and on-patent vaccines
In 2020, GSK donated more than 200,000 units of its branded amoxicillin/clavulanic acid (Augmentin®) towards humanitarian relief efforts run by charitable organisations, including Save the Children. In 2020, GSK supplied 56 million doses of its on-patent pneumococcal conjugate vaccine (Synflorix®) to Gavi-eligible countries. GSK supplied 115,000 doses of Synflorix® to refugee programmes run by MSF in Greece, Syria and South Sudan.

Pfizer: on-patent antibiotics and antifungals
In 2020, Pfizer reached 18,500 Brazilian and 2,500 Colombian patients with its on-patent antibiotics ceftazidime/avibactam (Zavicefta™) and ceftaroline (Zinforo®). In India, Pfizer reached 9,300 patients with Zavicefta™ and the antifungal isavuconazole (Cresemba®).

Cipla and Sun Pharma: off-patent/generic medicines
In 2020, Cipla distributed colistin in 500 Indian hospitals, treating 20,000 patients in India per month. In South Africa, it provided access to azithromycin to 280,000 patients. In 2020 and 2021, Cipla participated in a tender to distribute more than one million tablets of Q-TIB, a fixed dose combination used in tuberculosis prevention for people living with HIV, in seven LMICs including Haiti, Rwanda and Uganda. In 2020, Sun Pharma estimates that it provided access to its amoxicillin/clavulanic acid to 890,000 patients in 19 LMICs, including Cameroon, Myanmar, and Peru.

APPROPRIATE ACCESS – CASE STUDIES

What approaches are companies using to improve access to specific medicines and vaccines?

When it comes to access to medicine, there is no 'one-size-fits-all-products' approach. For each product, pharma companies, often working with partners from the global health community, must build tailored approaches and take account of a wide variety of factors. These range from commercial concerns such as patent status, and cover product characteristics – such as pack size, whether a vaccine needs a cold-chain, or whether it needs to be administered by trained health professionals. Importantly, the companies must address the needs and circumstances of specific populations, including their ability to pay. When the products in question are antimicrobials, the question of responsible use must also be front and centre of all decisions, to minimise the risk of drug resistance and ensure sustained effectiveness.

In this section, the Benchmark looks at examples of specific medicines and vaccines, some on-patent and some off-patent, to explore how pharmaceutical companies are expanding access to specific products.

CASE STUDY 1: IMPROVING ACCESS TO ON-PATENT VACCINES

Products: 18 vaccines from four large research-based companies. These include vaccines against pneumococcal disease, meningococcal disease, diphtheria, tetanus, and pertussis.

Why do vaccines need a different approach for improving access, compared to medicines?
Vaccines are a cornerstone of the modern health care system. Vaccination is an important component of primary health care and an indisputable human right. Vaccines are also an important tool against antimicrobial resistance. Yet despite tremendous progress, far too many people in the world - including nearly 20 million young children each year - still lack adequate access to vaccines. Most unvaccinated children live in low- and middle-income countries (LMICs), where health systems are often under pressure. 17 million children missed out on life-saving diphtheria and tetanus vaccines in 2020, and pneumonia kills more children each year than any other disease. Safe and affordable vaccines are the best way to prevent these infections.[6,7]

How do LMICs typically gain access to vaccines?
Vaccines are usually procured supranationally: they are purchased from multilateral organisations, such as Gavi, The Vaccine Alliance, The Pan American Health Organization (PAHO), and UNICEF. Gavi supports vaccines against 17 infectious diseases, including pneumococcal conjugate vaccine (PCV), in 57 countries, and has helped vaccinate more than 822 million children in the world's poorest countries, averting more than 14 million preventable deaths.[8] The Advance Market Commitment (AMC) for pneumococcal vaccines has enabled the procurement of a total of 161 million doses of PCV for lower-income countries.

Companies can also distribute their vaccines through national immunisation programmes initiated by local governments, such as in India or Thailand, often through a competitive bidding process with specific terms on prices, quantities, delivery, and contract duration. In humanitarian emergencies, vaccines can be distributed through humanitarian organisations, such as Médecins Sans Frontières (MSF).

How are prices negotiated?
Pneumococcal vaccine prices are negotiated between companies and UNICEF under the Advance Market Commitment and are made available to Gavi countries at a maximum price of $2.90 per dose. GSK and Pfizer have agreed to freeze prices for their pneumococcal vaccines (Synflorix® and Prevnar 13®) in Gavi-graduated countries for up to 10 years after graduation. For most vaccines, companies also apply tiered pricing policies that allow them to adjust the prices of their vaccines to countries' ability to pay, setting higher prices in middle- and high-income countries and offering

lower prices in low-income countries. In LMICs not supported by pooled-procurement mechanisms such as Gavi, PAHO or UNICEF, companies still have a responsibility to ensure that ability to pay is taken into account.[9]

How are companies involved?
Companies play an active role in expanding access to their vaccines. All vaccine manufacturers in scope apply a tiered pricing strategy for their vaccines, which allows for pricing flexibility. However, except for prices for pneumococcal vaccines distributed through Gavi (Synflorix® and Prevnar 13®), companies do not yet transparently disclose the prices of their vaccines in LMICs.

How does this approach help ensure supply can match demand?
The development and production of vaccines is usually complex. Gavi works closely with its industry partners, including GSK and Pfizer, to provide vaccines with forecasts of up to five years for large volumes. For their part, companies can improve production scale by offering new packaging features with multi-dose vials. Improving the production line can also reduce manufacturing costs and lead to lower selling prices.

CASE STUDY 2: NOVARTIS' APPROACH TO EXPANDING ACCESS TO OFF-PATENT MEDICINES

Products: Amoxicillin and amoxicillin/clavulanic acid, off-patent antibiotics produced by Novartis

How: Novartis uses equitable and competitive pricing and participates in tenders.

Impact: Amoxicillin is used to treat a variety of common bacterial infections, such as pneumonia, dental abscesses, and urinary tract infections.[10] Novartis reached more than 10 million people in LMICs to date.

Where: Novartis Healthy Family programmes are active in India, Kenya, Uganda and Vietnam.[11] Novartis Sub-Saharan African Unit (SSA) reaches 45 of the countries in scope.

Details: Novartis, through Novartis Access, Novartis Healthy Family and Novartis SSA, offers its generic antibacterial products at tailored prices to governments, non-governmental organisations and other institutional customers in lower-income countries. Novartis's access pricing policy means prices start at USD 1 per treatment, per month. Its SSA unit takes a high-volume, low-price approach to increasing patient reach. In 2020, more than four million patients in eligible countries were ensured access to amoxicillin through Novartis Access and Novartis Healthy Family. More than 1.7 million patients were ensured access to amoxicillin and amoxicillin/clavulanic acid through Novartis SSA Unit in the public sector.

Novartis has publicly set a goal to increase patient reach two-fold by 2022 and five-fold by 2025 through its SSA unit. In 2020, Novartis, through its Sandoz division, committed to selling some of its medicines, including antibiotics used to treat patients with COVID-19-related symptoms, at zero-profit to governments in up to 79 eligible low-income and lower-middle-income countries.

Novartis participates in competitive bidding. Tender prices are set using Novartis's cost of goods with an additional minimum acceptable margin, as well as historical data and local insights from its customers. Making use of local insights may include considering the most recently awarded prices, the most recently awarded companies, and the maximum tender price set by the relevant National Health Insurance Scheme.

CASE STUDY 3: PFIZER'S DONATION PROGRAMMES FOR OFF-PATENT MEDICINES

Pfizer, Azithromycin (Zithromax®) Donation programme
Pfizer is part of the International Trachoma Initiative (ITI), established in 1998. In 2020, 31.1 million treatments were shipped to 12 countries through the ITI. As of April 2020, nine countries in scope have been validated by WHO as having eliminated trachoma as a public health problem. These countries are Cambodia, China, Lao People's Democratic Republic, Ghana, Mexico, Morocco, Myanmar, Nepal, and – most recently – Gambia. More than 95 million people have benefited from Pfizer's donation programme. Pfizer extended its donation programme until 2025, to align with WHO's new target date of 2030 for global trachoma elimination.

Pfizer, fluconazole (Diflucan®) Partnership programme
Pfizer and its partners have distributed more than seven million doses of fluconazole (Diflucan®) to governments and non-governmental organisations (NGOs) over the past two years to people suffering from AIDS-related fungal infections, such as cryptococcal meningitis and esophageal candidiasis. Nine countries in scope are benefiting from this donation programme, including Botswana, Cameroon, Malawi, Rwanda, Swaziland, and Lesotho.

CASE STUDY 4: GENERIC MEDICINES MANUFACTURERS' APPROACH TO EXPANDING ACCESS TO OFF-PATENT/GENERIC MEDICINES

Companies: Aurobindo, Fresenius Kabi, Teva

How: Aurobindo and Fresenius Kabi mainly distribute their off-patent/generic medicines through tenders or direct-selling contracts. Teva stands out for its product donations.

Where: Global-scale, Malawi

Details: Aurobindo applies affordable pricing policies for its off-patent antibacterial and antifungal medicines in all sales segments and participates in tenders in countries where its medicines are registered. Tenders can be an effective tool for governments to obtain discounts.

Fresenius Kabi makes its generic medicines available in hospitals in the countries in which it operates, mainly by participating in tenders or through direct sales contracts with hospitals.

In many countries, generic medicines are subject to mandatory price control mechanisms, that result in lower prices compared to originator medicines.

Teva is partnering with Global HOPE and Direct Relief to donate antibiotics to paediatric immunocompromised cancer patients in Malawi. The goal of the initiative is to treat 4,000 paediatric patients in Malawi over the next five years.

CASE STUDY 5: EXPANDING ACCESS TO TB MEDICINES

Products:
MDR-TB* medicine bedaquiline (Sirturo®) – Johnson & Johnson
MDR-TB medicine delamanid (Deltyba®) – Otsuka and Viatris
M/XDR-TB** pretomanid (Dovprela) – Viatris

How: Most TB medicines are procured via the GDF-Stop TB Partnership, which ensures that national TB control programmes have uninterrupted access to quality-assured medicines by providing direct procurement services and securing competitive prices, contingent on good stewardship practices. Companies can also use additional access strategies to reach people in poorer countries directly, such as voluntary licensing agreements, patient assistance programmes, or bidding in national tenders.

Impact: Since its creation in 2001, the Global Drug Facility (GDF) has facilitated access to TB medicines and diagnostics in more than 140 countries, making quality-assured treatments available to over 32 million people with TB. GDF supplies longer and shorter all-oral regimens for drug-resistant TB, and child-friendly medicines for both drug-sensitive and drug-resistant TB. GDF has secured price reductions of over 50% for most drug resistant tuberculosis (DR-TB) medicines, primarily by reducing risks to suppliers and minimising their transaction costs. 128 countries have received drug-sensitive TB medicines via the GDF since its inception, reaching almost 34 million adults and 2.5 million children.[12]

Where: Up to 150 countries and territories – including all 102 LMICs in the Benchmark's scope – are eligible for the 'access' price for bedaquiline, delamanid and pretomanid when procuring via GDF. Companies reported country-specific donations and patient assistance programmes (e.g., in India and South Africa) and responding to both country and GDF global tenders.

Details:
GDF-Stop TB Partnership provides the on-patent TB medicines in scope of the Benchmark at defined global access prices. Bedaquiline is priced at US$340 per six-month treatment course with an escalating percentage of free goods depending on volume thresholds, resulting in a prorated price of US$272 per six-month treatment in 2021. Per six-month treatment-course, pretomanid is priced at US$364, and delamanid at US$1700.

Otsuka has geographically exclusive licensing agreements with Viatris and R-Pharm. Viatris received a technology transfer from Otsuka, allowing it to produce delamanid in India. However, the delamanid produced by Viatris does not currently meet quality assurance requirements of donors, as it is not approved by a Stringent Regulatory Authority or the WHO Prequalification Programme.

Viatris has agreed to donate 400 cumulative treatment courses of pretomanid directly to the Indian National Tuberculosis Elimination Programme and to the South African Conditional Access Programme.

In April 2021, Viatris also launched a named patient access programme to provide access to individual patients in countries where pretomanid is not yet registered or available, free of charge or on par with GDF access pricing, depending on eligibility.

* Multidrug-resistant tuberculosis
** Multidrug- and extensively drug-resistant tuberculosis

APPROPRIATE ACCESS – SUPPLY

What steps are pharma companies taking to ensure continuous supply?

To reduce the threat of AMR, the right treatment must be used to treat the right type of infection. Yet antibacterial supply chains are complex and highly fragmented. Batches of medicines and vaccines pass through multiple distributors with little alignment to ensure continuous supply. These inefficiencies can lead to stock-outs, while the fragmentation of the supply chain is a driving factor for shortages. The Benchmark evaluates the steps companies are taking to deliver an uninterrupted supply of quality products.

Supply chain challenges

Global antibiotic supply chains are highly fragmented, consisting of many players at some stages of the chain, and very few at other vital stages. Supply inefficiencies can be caused by failures in manufacturing processes, scarcity of active pharmaceutical ingredients (APIs), the concentration of API manufacturing in only a few countries (mainly India and China), pressure on margins, and heavy dependence on only one or a few producers of some antibiotics.

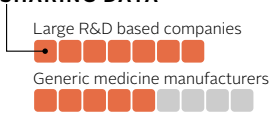
FIGURE 53. **What are companies doing to ensure a continuous supply of antibiotics, antifungals and vaccines?**

This table lists the priority activities for companies to help ensure the uninterrupted supply of their products, along with examples of company activity in each area.

FORECASTING DEMAND

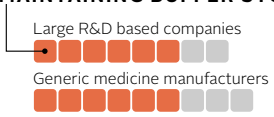
How: To maintain a continuous supply of products, companies make use of short- and long-term forecasting mechanisms to ensure there are sufficient APIs and finished products to meet future demand for those products.
Example: Aurobindo makes a monthly rolling forecast and monitors supply in some countries on a weekly basis. Aurobindo also uses long-range planning to provide medium- to longer-term forecasts.

SHARING DATA



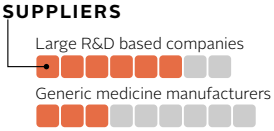
How: Companies exchange information with external stakeholders (such as government ministries of health) to align supply with demand.
Example: Novartis ensures that forecasts for all countries are carried out according to a standardised - at least monthly rolling - process, 1-36 months in advance. The company ensures weekly data exchange with its anti-infective stakeholders.

MAINTAINING BUFFER STOCKS



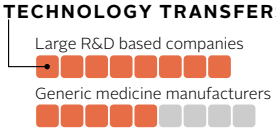
How: To mitigate against shortages, companies can maintain a buffer stock of extra inventory in case of manufacturing delays or an unexpected increase in demand.
Example: Abbott maintains a buffer stock of critical APIs and finished goods that is reviewed quarterly and adjusted as needed.

WORKING WITH SEVERAL API SUPPLIERS



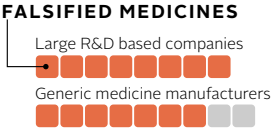
How: To mitigate against shortages, companies can work with several API suppliers.
Example: The APIs in Viatris' products are sourced from third parties or manufactured internally. Viatris has a global supply network consisting of more than 40 locations worldwide, including for the antibacterial and antifungal agents in scope. The company registers several of its products in multiple locations to mitigate the risk of shortages, and to allow flexibility to meet demand.

CAPACITY BUILDING AND/OR TECHNOLOGY TRANSFERS



How: To support the development of local manufacturing in low- and middle-income countries (LMICs), pharma companies can invest in capacity building and technology transfers – whereby skills, knowledge, technologies, and manufacturing methods are shared with local manufacturing partners.
Example: Otsuka is ensuring a technology transfer to Viatris (previously Mylan) for delamanid (Deltyba®). The first phase of the technology transfer was completed in 2020, allowing Viatris to manufacture, package, and distribute delamanid in its own access countries. The second phase of the technology transfer for full API manufacturing is on-going and expected to be completed in 2021. Following this technology transfer, Viatris' manufactured delamanid has been made available in a number of LMICs, including South Africa and India, and will be available for procurement through the GDF following WHO prequalification.

MITIGATING AGAINST SUBSTANDARD & FALSIFIED MEDICINES



How: Companies prevent or mitigate the production or supply of medicines that appear to be authentic, but are of low quality or contain replacement and/or non-working ingredients.
Example: Sanofi has several structures, governance and policies dedicated to fighting substandard and falsified products. These include a pharmaceutical crime investigation department, an anti-counterfeiting coordination network, a security department that helps detect illegal sales on the Internet, and a dedicated central laboratory in France for analysis of falsification. If a substandard and falsified product is identified, it will be reported to the relevant local authorities within seven days and a market withdrawal may be decided. If necessary, doctors, pharmacists and patients may also be informed. Investigations and legal action may be taken to identify the origin of the substandard and falsified product.

How are companies ensuring a continuous supply of their products in LMICs?
Accessibility relies on companies having strategies to ensure a continuous supply of antibacterial and antifungal medicines and vaccines, both on- and off-patent. To ensure an uninterrupted supply of high-quality products, companies need to prepare for stockouts by ensuring the supply of active pharmaceutical ingredients (APIs), keeping sufficient buffer stock, and aligning with external stakeholders on supply and demand. When people are assured of a continuous supply, this decreases the chance they will resort to obtaining substandard or falsified medicines and thereby increasing the risk of AMR.

KEY TERMS

A **stockout** occurs when a doctor or pharmacist cannot dispense an antibiotic because there is no stock available in that location, at that time.

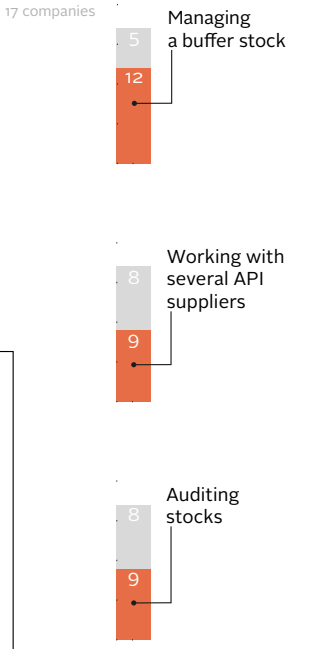
A **shortage** occurs when supply does not meet demand. Shortages can occur on a national level (i.e., when specific regions or countries cannot bring in supplies for any reason), or at a global level (i.e., when all countries struggle to access the medicine).

FIGURE 54. **What steps are pharma companies taking to ensure continuous supply?**
This table shows the activities which the companies report using to ensure the uninterrupted supply of their products.

	Demand planning and data sharing activities	Capacity building and/or technology transfers inititiaves	Strategies to mitigate against substandard and falsified medicines	Strategies to mitigate against risk of shortages
Large research-based companies				
GSK	●	●	●	●
Johnson & Johnson	●	●	●	●
MSD	●	●	●	●
Novartis	●	●	●	●
Otsuka	●	●	●	●
Pfizer	●	●	●	●
Sanofi	●	●	●	●
Shionogi	○	●	●	○
Generic medicine manufacturers				
Abbott	●	●	●	●
Alkem	○	○	○	○
Aurobindo	●	●	●	●
Cipla	●	●	●	●
Fresenius Kabi	●	●	●	●
Hainan Hailing	○	○	○	○
Viatris	●	●	●	●
Sun Pharma	●	○	●	●
Teva	●	○	●	●

● Activity reported ○ No activity reported

FIGURE 55. **Focus on different strategies to mitigate against risk of shortages**
This figure shows three approaches used by the companies to reduce the risk of shortages, and how many companies use each one.



Sanofi has publicly set a "zero out of stock" goal. The company has a consistent safety stock policy to ensure the right level of safety stock in countries. Its supply chain data is locally adjusted and adapted for low- and middle-income countries.

APPROPRIATE ACCESS – TECHNOLOGY TRANSFERS

Companies carry out global tech transfers as isolated, yet valuable, initiatives

Medicines and vaccines are produced via sensitive, multi-stage, and highly technical processes. To give an idea of the complexity, it can take more than a year to complete all manufacturing and quality steps for a single batch of vaccines. It is important that multiple manufacturers can master these processes – to make sure supply can meet demand everywhere in the world, and to minimise the impact of a shutdown of a single manufacturing site. Further, when medicines and vaccines are produced locally, the shorter supply chains help lower the risk of regional shortages.

To support the development of local manufacturing in low- and middle-income countries, pharma companies can invest in capacity building and technology transfers – whereby the skills, knowledge, technologies, and manufacturing methods are shared with local manufacturing partners.

Of the 18 on-patent vaccines included in this analysis, nine are subject to a technology transfer initiative; by contrast, very few initiatives covering any of the 148 on-patent and off-patent medicines (antibiotics and antifungals) have been reported to the Benchmark. Medicines which are covered by an initiative include tuberculosis products, as well as some older antibiotics – including one 'Watch' antibiotic.

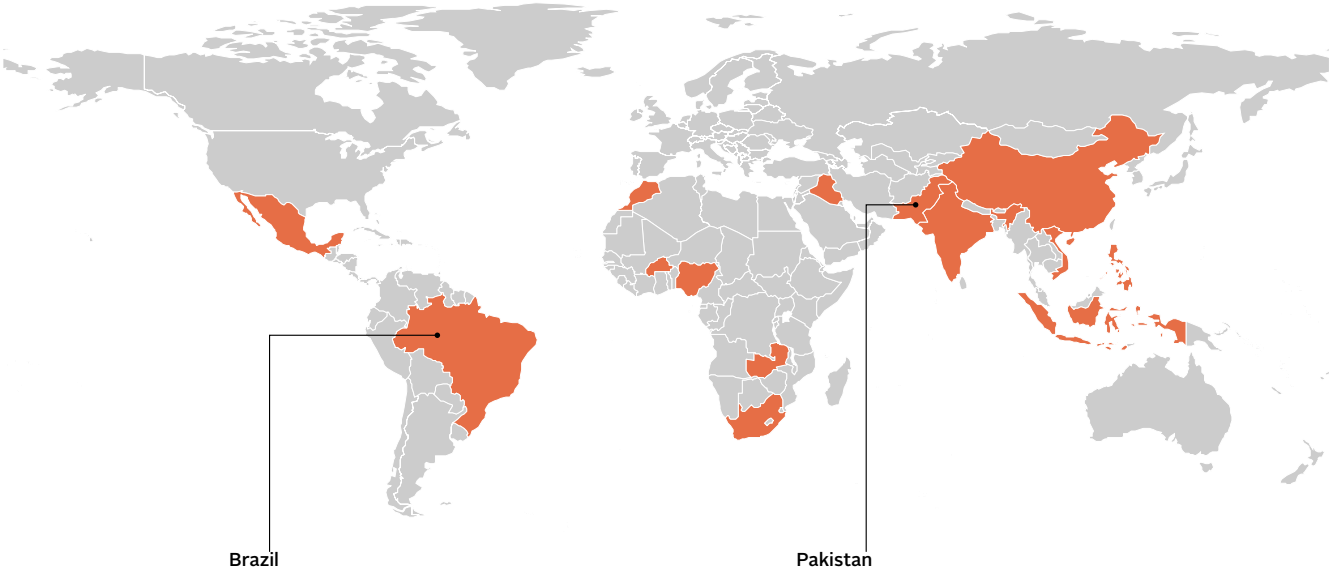
KEY TERMS

Technology transfer
A pharma company transfers knowledge about the process to make a specific medicine or vaccine to a manufacturing site in a country where that product is needed, along with the technology necessary to manufacture it.

Capacity building
Building manufacturing or supply chain capacity by working with local partner manufacturers, distributors, and logistics providers to identify bottlenecks and improve capacity for appropriate supply chain and manufacturing management.

Local manufacturing sites
Pharmaceutical companies can invest in local manufacturing facilities to produce raw ingredients and/or finished products, by financing and building reliable infrastructures and helping staff develop technical expertise.

FIGURE 56. **10 pharma companies support local manufacturing projects across 14 LMICs**
Of the 17 companies covered by the Benchmark, 10 report that they are supporting local manufacturing (such as by carrying out technology transfers) in at least one of the 102 low- and middle-income countries in scope. This map shows the countries where at least one project is taking place.



Brazil
GSK partners with three Brazilian state-owned vaccine manufacturers to produce its priority vaccines, including antibacterial vaccines, locally in Brazil. Three activites are covered by this technology transfer: 1) manufacturing pratices, such as formulating and packaging; 2) technical know-how; and 3) analytical testing methods. This technology transfer aims to upgrade the infrastructure, develop local manufacturing capabilities, and train employees in good manufacturing practices. Brazil should be able to produce at least 60 million vaccine doses for its population each year.

Pakistan
In Pakistan, Novartis is partnering with local third parties to produce some of its products locally, including its Sandoz penicillin portfolio, and transfer manufacturing knowledge. This technology transfer aims to promote local manufacturing capacity, and to enable those manufacturing sites to meet manufacturing practice standards, improve levels of technical capability, and comply with health, safety, and environmental (HSE) regulations.

Zoom-in on technology transfers and manufacturing in Africa

Africa accounts for nearly 17% of the world's population, but produces only 3% of the medicines and 1% of the vaccines it consumes. Most of the medicines and vaccines distributed must be imported from producers in foreign countries such as India and China, which means they pass through multiple distribution channels and intermediaries. Up to half of the patients in Africa are estimated to lack access to critical medicines.[13] In sub-Saharan Africa, only Kenya, Nigeria, and South Africa have a relatively sizeable industry, with several companies that produce for their local markets and, in some cases, for export to neighbouring countries.[14]

Even though supply chains remain international and fragmented, and countries may still need to source raw materials, active ingredients, or excipients from abroad, pharma companies can continue to build sustainable initiatives to enable more countries and regions to produce their own medicines and vaccines locally in the long term.

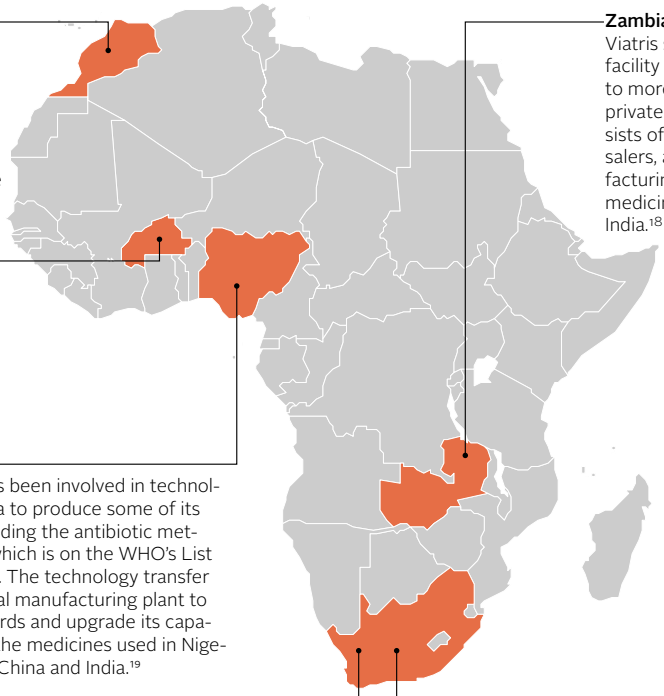
A collaborative approach is needed

Lack of capability and training are significant challenges. Companies that demonstrate best practice often partner with others, and/or open their own offices locally. They also work with other stakeholders (such as governments and NGOs) to plan transfers of technology to enable products to be made sustainably.

Pharmaceutical companies' decisions to transfer technology depends on a variety of factors, such as finding a local partner, local politics and market environment, political stability, or good regulatory standards. While low-income countries are not always able to meet these conditions, stable and industrialised upper-middle-income and lower-middle-income countries may present an opportunity for successful technology transfer.[21]

FIGURE 57. **Countries in Africa where technology transfers are being carried out**

Seven of the 17 companies evaluated report that they are carrying out at least one technology transfer project in at least one African country. These projects are spread across five countries.



Morocco
One company, whose name cannot be disclosed, is carrying out a technology transfer to a third-party manufacturer for the production of active pharmaceutical ingredients (APIs) for antibiotics. Morocco manufactures 70% of the pharmaceutical products it consumes, but depends largely on foreign supply of raw materials, and imports more than 90% to meet these needs.[15]

Burkina Faso
One company, whose name cannot be disclosed, is carrying out a technology transfer to a third-party manufacturer for the production of APIs for antibiotics. Burkina Faso is heavily reliant on imported pharmaceutical products to meet the needs of its population.[16]

Nigeria
Since 2008, Sanofi has been involved in technology transfers in Nigeria to produce some of its medicines locally, including the antibiotic metronidazole (Flagyl®), which is on the WHO's List of Essential Medicines. The technology transfer aims to enable the local manufacturing plant to meet all quality standards and upgrade its capabilities. About 70% of the medicines used in Nigeria are imported from China and India.[19]

Zambia
Viatris supports a manufacturing facility in Zambia. In Zambia, home to more than 17 million people[17], the private pharmaceutical sector consists of local manufacturers, wholesalers, and retailers. Local manufacturing capacity is very small, and medicines are mainly imported from India.[18]

South Africa
Seven companies are involved in technology transfers in South Africa. The country has a diverse economy with an established and well-developed manufacturing base, which helps explain why it benefits from the most reported technology transfer initiatives. However, although South Africa is an upper-middle-income country, it is a dual economy with one of the highest persistent inequality rates in the world, and thus remains an important focus for access to medicine.[20]

South Africa
Pfizer is working with the South African government and Biovac Consortium Cape Town to produce its pneumococcal vaccine (Prevnar13®) locally, from raw materials all the way through to packaged products. Pfizer has developed automated processes to standardise the complex formulation of the vaccine, which helps facilitate the technology transfer and reduces manufacturing risks.

APPROPRIATE ACCESS

Looking ahead

While the Benchmark identifies little forward movement on access to antimicrobials and antifungals in low- and middle-income countries (LMICs), there are tangible steps which companies can take. This page outlines what different groups of stakeholders can do, from companies to governments.

COMPANIES

Registration

- Register medicines and vaccines more widely, or, when applicable, use an alternative option of special import waivers in order to facilitate access.
- Focus on registering products in countries where the number of registered products is the lowest, and where the burden of diseases is highest, in order to reach those who are most in need.

Access strategies

- Consider the full range of access strategies from the toolkit to determine what is most appropriate, such as voluntary licensing, partnering with external stakeholders, patient assistance programmes, and equitable pricing policies.
- Take affordability into account, ensuring that their medicines and vaccines are affordable to the most people, including in the poorest countries.
- Set specific Key Performance Indicators (KPIs) to assess the impact of access strategies, such as by measuring patient reach.

Ensuring continuous supply

- Reduce the risk of shortages by aligning with external stakeholders to keep sufficient buffer stocks, and by working with several API manufacturers to ensure non-interrupted supply. This will also help prevent substandard and falsified products from reaching LMICs.
- Build sustainable initiatives to enable more countries and regions to produce their own medicines and vaccines locally over the long term, in the form of local manufacturing facilities, regional hubs, and technology transfers.

GOVERNMENTS

- Build capacity within local regulatory health authorities to strengthen and expedite the processing of dossiers and the approval of products, in order to encourage more companies to file products for registration. Participate in the World Health Organization's collaborative product assessment and regional regulatory harmonisation initiatives.
- Support advocacy for increased transparency around which products have been filed or approved for registration with a country's regulatory health authority. Regulatory health authorities should make this information accessible themselves by publishing it in the public domain.
- Support the building of local manufacturing capacity to encourage technology transfers for the production of safe, high-quality medicines and vaccines in LMICs. Create a supportive environment for domestic industry.
- Where appropriate, participate in pooled procurement mechanisms, (e.g., on a regional basis) in order to help secure volume commitments and build stronger and more enticing markets for companies.
- Support collaborative registration procedures and mechanisms such as the African Medicines Agency, to help streamline and expedite registration filings and approvals.
- Foster a stable market for, and support initiatives to ensure appropriate access to, existing older off-patent antibiotics and antifungals. This will discourage companies from discontinuing such products, many of which are still effective – but are not always available in LMICs.

REFERENCES

1. The Access to Medicine Foundation. Biotechs Are Saving the World from Superbugs. Can They Also Save Themselves?; 2021. Accessed October 12, 2021. file: https://accesstomedicinefoundation.org/publications/biotechs-are-saving-the-world-from-superbugs-can-they-also-save-themselves

2. Access to Medicine Foundation. 2020 Antimicrobial Resistance Benchmark - Access to Medicine Foundation. Published 2020. Accessed October 21, 2021. https://accesstomedicinefoundation.org/publications/2020-antimicrobial-resistance-benchmark

3. Access to Medicine Foundation. The Methodology for the 2021 Antimicrobial Resistance Benchmark - Access to Medicine Foundation. Published 2020. Accessed October 21, 2021. https://accesstomedicinefoundation.org/publications/the-methodology-for-the-2021-antimicrobial-resistance-benchmark

4. Johnson & Johnson. Bedaquiline Country Regulatory Status Overview. Published 2021. Accessed October 21, 2021. https://www.jnj.com/_document/bedaquiline-country-regulatory-status-overview?id=0000016e-0467-db13-a9ef-566f1a520000

5. Micoli F, Bagnoli F, Rappuoli R, Serruto D. The role of vaccines in combatting antimicrobial resistance. Nat Rev Microbiol 2021 195. 2021;19(5):287-302. doi:10.1038/s41579-020-00506-3

6. World Health Organization. Vaccines and immunization. Published 2021. Accessed October 21, 2021. https://www.who.int/health-topics/vaccines-and-immunization#tab=tab_1

7. Access to Medicine FOundation. Access to Vaccines Index 2017 How vaccine companies are responding to calls for greater immunisation coverage. Published online 2017. Accessed October 21, 2021. www.accesstomedicineindex.org

8. Gavi The Vaccine Alliance. About our Alliance. Published 2021. Accessed October 21, 2021. https://www.gavi.org/our-alliance/about

9. Gavi The Vaccine Alliance. Pneumococcal vaccine support. Published 2021. Accessed October 21, 2021. https://www.gavi.org/types-support/vaccine-support/pneumococcal

10. NHS. Amoxicillin: antibiotic to treat bacterial infections - NHS. Published 2021. Accessed October 21, 2021. https://www.nhs.uk/medicines/amoxicillin/

11. Novartis. Healthy Family Programs . Published 2021. Accessed October 21, 2021. https://www.novartis.com/esg/access/creating-sustainable-business-models/healthy-family-programs

12. World Health Organization. Tuberculosis. Published 2021. Accessed October 21, 2021. https://www.who.int/news-room/fact-sheets/detail/tuberculosis

13. Africa Resource Center. About Us, Africa Resource Center. Published 2021. Accessed October 21, 2021. https://www.africaresourcecentre.org/about-us/

14. McKinsey & Company. Evaluating the sub-Saharan African pharmaceutical market | McKinsey. Published 2019. Accessed October 21, 2021. https://www.mckinsey.com/industries/public-and-social-sector/our-insights/should-sub-saharan-africa-make-its-own-drugs

15. Health Action International WHO. Medicine prices and access to medicines in the Eastern Mediterranean Region Presentation of price information. Published online 2008. Accessed October 21, 2021. http://www.haiweb.org/

16. Africa Resource Center. Strengthening medicine supply planning in South Africa during COVID-19. Published 2021. Accessed October 21, 2021. https://www.africaresourcecentre.org/strengthening-medicine-supply-planning-during-covid19/

17. The World Bank. Zambia | Data. Published 2021. Accessed October 21, 2021. https://data.worldbank.org/country/zambia

18. Handema R, Kandeke C, Lupuma A, Lishimpi L, Yeta C. Measuring Transparency to Improve Good Governance in the Public Pharmaceutical Sector ZAMBIA. Published online 2012.

19. Awucha NE, Janefrances OC, Meshach AC, Henrietta JC, Daniel AI, Chidiebere NE. Impact of the COVID-19 Pandemic on Consumers' Access to Essential Medicines in Nigeria. Am J Trop Med Hyg. 2020;103(4):1630. doi:10.4269/AJTMH.20-0838

20. The World Bank. South Africa Overview: Development news, research, data | World Bank. Published 2019. Accessed October 21, 2021. https://www.worldbank.org/en/country/southafrica/overview#1

21. International Federation of Pharmaceutical Manufacturers & Associations. The Research-Based Pharmaceutical Industry Experience. Published online 2015.

CONTEXT

Stewardship

One of the main factors driving drug resistance is the misuse and overuse of antibacterial and antifungal medicines. Specific strategies are needed to ensure such medicines are used only when appropriate, in order to reduce opportunities for pathogens to develop new ways of withstanding the medicines. While the success of these 'stewardship' strategies often depends on actions taken by governments, prescribers and pharmacists, there is also a clear role for pharmaceutical companies. This role encompasses how they package and sell their products, and how they carry out 'surveillance' to track the emergence and spread of resistance.

Growing consumption drives resistance

Between 2000 and 2010, the consumption of antibiotics grew by more than a third across 71 countries.[1] This was mainly driven by increases in consumption in Brazil, Russia, India, China and South Africa – countries which face some of the highest rates of resistance.

Stewardship is needed worldwide

Robust safeguards to protect the effectiveness of antibacterial and antifungal medicines must be instituted worldwide to ensure that these medicines remain effective. For example, antibiotics should be prescribed only when needed, and certain antibiotics should only be prescribed as a last resort.

HOW PHARMA COMPANIES CAN BOLSTER RESPONSIBLE USE OF THEIR MEDICINES

Surveillance

Pharmaceutical companies gather data that indicate where infection rates are rising, and where resistance is emerging. These insights are valuable puzzle pieces, particularly where they cover countries without national surveillance efforts. For example, they can inform the treatment guidelines used by doctors when making clinical decisions.

Sales practices

When sales agents' bonuses are linked to the quantity of antibacterial and antifungal medicines they sell, it acts as an incentive for those agents to oversell. Companies can minimise the risk of overselling by removing the link between sales volume and financial rewards, or even by stopping the use of sales agents for antibacterials and antifungals.

Conflict of interest

Pharmaceutical companies have a deep understanding of how their medicines can be used responsibly and appropriately. Where companies contribute to educational activities for healthcare professionals on how best to manage the risk of resistance while using their products, they must also pro-actively avoid conflicts of interest.

Adherence

The risk of resistance is kept to a minimum when patients can understand and adhere to their courses of treatment until they are completed. Through the information they provide on packaging and brochures – as well as by wider campaigns to raise awareness of drug resistance – pharma companies can encourage the appropriate use of their medicines.

Companies in scope

The 2021 AMR Benchmark examines the policies and practices of eight large research-based companies and nine generic medicine manufacturers (see list, right) in supporting the appropriate stewardship of their medicines. By volume and value of sales, these are among today's largest players in the global market for antibacterial medicines, together accounting for 29,031.60 SU million doses sold annually.* This gives them significant opportunities to understand whether their products are being used appropriately and responsibly.

Countries in scope

In regards to stewardship, the geographic scope of the Benchmark's analysis is global.

Pathogens in scope

In terms of surveillance, the Benchmark highlights "priority pathogens" identified as posing the greatest risk to human health from AMR. These are the bacteria and fungi identified by the World Health Organisation (WHO) and/or the US Centers for Disease Control and Prevention (CDC) as priority R&D targets for limiting AMR.**

Companies in scope for Stewardship

	Large research-based companies	Country HQ
1	GlaxoSmithKline plc	GBR
2	Johnson & Johnson	USA
3	Merck & Co, Inc	USA
4	Novartis AG	CHE
5	Otsuka Pharmaceutical Co, Ltd	JPN
6	Pfizer Inc	USA
7	Sanofi	FRA
8	Shionogi & Co, Ltd	JPN

	Generic medicine manufacturers	
1	Abbott Laboratories	USA
2	Alkem Laboratories Ltd	IND
3	Aurobindo Pharma Ltd	IND
4	Cipla Ltd	IND
5	Fresenius Kabi AG	DEU
6	Hainan Hailing Chemipharma Corp Ltd	CHN
7	Viatris***	GBR
8	Sun Pharmaceutical Industries Ltd	IND
9	Teva Pharmaceutical Industries Ltd	ISR

* Source: IQVIA Midas 2017 anti-infectives data. Companies with sales volumes below 1.000 SU million are not included in this number.
** See appendix V.
*** Mylan has been renamed Viatris, following closing of merger with Upjohn, a division of Pfizer, in 2020.

STEWARDSHIP – SURVEILLANCE

Most companies support global efforts to track the spread of resistance

In order to control the spread of resistance, it is important to know where cases are occurring and where infection rates are rising. By monitoring resistance to treatment in patient populations around the world, the resistant strains can be identified and their subsequent spread can be addressed. Efforts to collect data on the emergence and spread resistance are termed 'AMR surveillance'.

To date, AMR surveillance has primarily been the responsibility of governments. However, pharmaceutical companies also have an important contribution to make. Companies often have unique knowledge of resistance trends, which are particularly valuable where their data cover countries without national surveillance efforts.

In 2020, the Benchmark reported an increase in the number of surveillance programmes being run by the pharmaceutical companies in its scope. It also reported that the majority of these programmes share their results publicly. In 2021, the Benchmark again compares the surveillance programmes of the eight large research-based companies in scope, and reports on whether they are active in the surveillance of bacterial or fungal pathogens and/or infections anywhere in the world and whether these results are shared publicly.

As in 2020, the 2021 Benchmark examines the stewardship activities of generic medicine manufacturers. However, these companies are not officially scored in this area, as they have thus far had a limited role in such activities.

Most companies are engaged in AMR surveillance programmes

As in the 2020 Benchmark, most companies are engaged in surveillance to some extent. Out of the eight large research-based companies, Otsuka remains the only company not involved. Three generic medicine manufacturers, namely Abbott, Cipla and Viatris, report that they are engaged in surveillance.

There are 19 programmes in which at least one company is engaged. Most of the programmes cover at least one priority pathogen.*

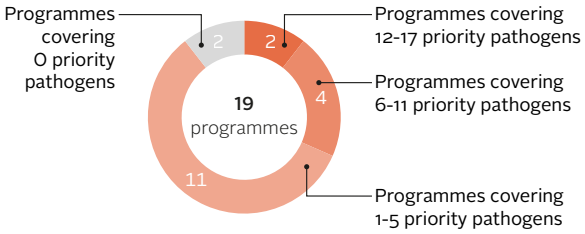
Sharing consumption data is important in overall surveillance activities

Tracking and monitoring data on how antimicrobials are being consumed plays an important role in reducing their misuse. Pharmaceutical companies can provide data to estimate consumption through their imports, sales, donations and production records, and this can enhance national surveillance of antimicrobial consumption.

Who is sharing consumption data?

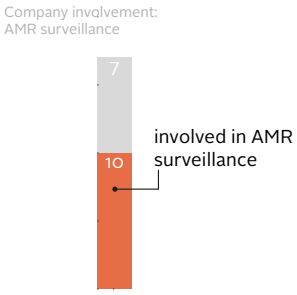
- GSK periodically shares consumption data on colistin and/or other antibacterial medicines with the Pharmaceuticals and Medical Devices Agency in Japan.
- Johnson & Johnson and Otsuka share some consumption data on their MDR-TB medicines bedaquiline (Sirturo®) and delamanid (Deltyba®), respectively, with national and international health organisations.
- Fresenius Kabi shares consumption data with national governments or other public health authorities, as appropriate. For example, it shares sales data on meropenem in Latin American countries.

FIGURE 58. **How many priority pathogens do the programmes cover?**
This figure shows the extent to which the programmes identified by the Benchmark cover the surveillance of priority pathogens.*



While most companies collect data on pathogens targeted by their own products, some companies go beyond by also focusing on priority pathogens*. These include Pfizer's ATLAS programme and CANWARD, which is managed by the Canadian Antimicrobial Resistance Alliance.

FIGURE 59. **How engaged are the companies in AMR surveillance?**
The chart below shows how many of the 17 companies assessed are engaged in AMR surveillance.



Seven of the eight large research-based companies support global AMR surveillance efforts, with the exception of Otsuka. Novartis is newly involved in surveillance. Three of the generic medicine manufacturers (Abbott, Cipla, Viatris) are also involved in surveillance.

* Bacteria and fungi identified as priority R&D targets for limiting AMR, by the WHO and/or the US Centers for Disease Control and Prevention (CDC). See Appendix V.

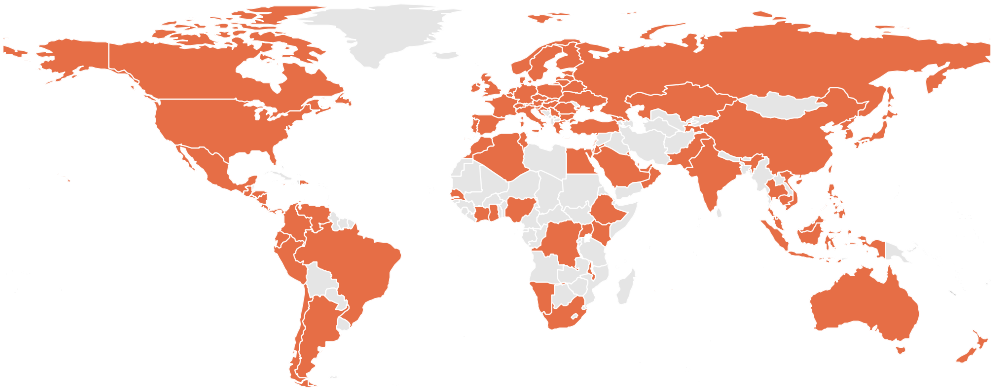
Geographic coverage of surveillance is variable in Central Asia and Africa

Each surveillance programme covers a different geographic scope and range of pathogens. There are many stakeholders around the world working to build as complete a picture as possible of where resistance is emerging, such as the WHO's Global Antimicrobial Resistance and Use Surveillance System (GLASS). Companies can fund external programmes run by established institutions, and they can also run their own surveillance programmes.

The first map below shows all countries covered by at least one of the 19 company programmes.

The two other maps below demonstrate, for two high-risk pathogens *Candida* spp. and *S. aureus,* how company data can provide information and where gaps remain in global surveillance.

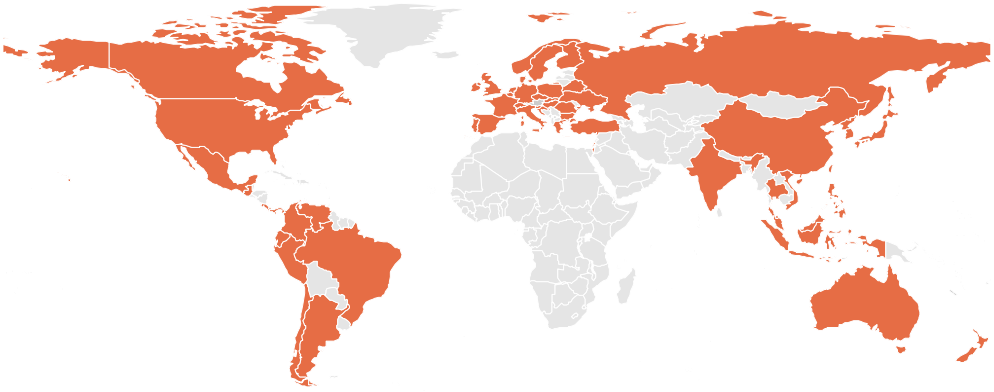
FIGURE 60. **Countries with at least one surveillance programme**



Programmes running: 19
Companies involved: 10

High-income countries are consistently covered by surveillance programmes, as are upper-middle income countries such as Brazil, China and India. Coverage in low- and lower-middle income countries in Central Asia and Africa, however, is more variable. For example, Iran is not covered despite having high rates of antimicrobial consumption as well as resistance against pathogens including. *E. coli* and *K. pneumoniae*.[2,3]

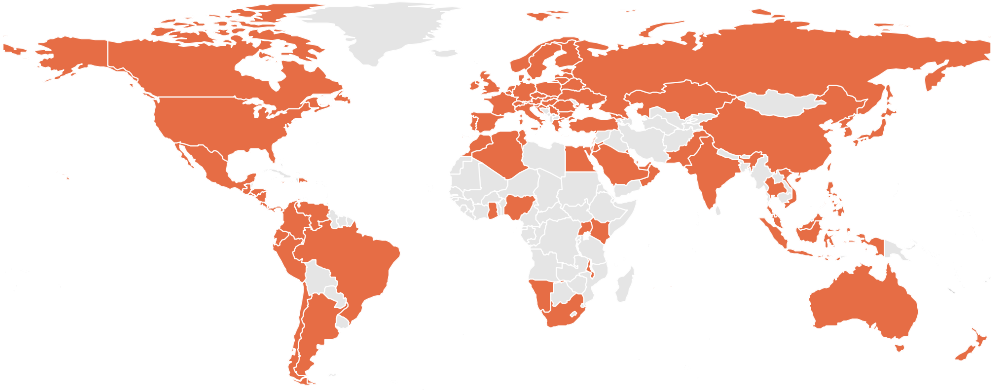
FIGURE 61. **Countries with at least one surveillance programme covering *Candida* spp.**



Programmes running: 3
Companies involved: 5

Candida spp. is a common cause of candidiasis. Notably, the entire continent of Africa is not covered by any programme across any of the companies in scope, despite increasing resistance rates of *Candida* spp. in Sub-Saharan Africa.[4]

FIGURE 62. **Countries with at least one surveillance programme covering *S. aureus***



Programmes running: 10
Companies involved: 6

S. aureus is a common cause of skin and soft tissue infections. In contrast to programmes covering *Candida* spp., *S. aureus* is covered in a few countries in Africa, but significant gaps remain.

* Bacteria and fungi identified as priority R&D targets for limiting AMR, by the WHO and/or the US Centers for Disease Control and Prevention (CDC). See Appendix V.

TABLE 8. **Overview of surveillance programmes, broken down by company and by priority pathogen**

The table shows all 19 AMR surveillance programmes in which pharmaceutical companies in scope are active, as well as which of the priority pathogens* are covered by each programme. *Enterobacteriaceae*, *P. aeruginosa*, *S. aureus* and *S. pneumoniae* are the priority pathogens most commonly under surveillance. The longest-running programme has been active since 1992, while two new programmes have started since the 2020 Benchmark. The geographic range varies widely, from 1 to 81 countries.

					'Critical' and/or 'Urgent' pathogens					'High' and/or 'Serious' pathogens								'Medium'; 'Concerning' and/or 'Watch' pathogens		
AMR surveillance programme	**Companies active**	**Start year**	**Geographic scope / number of countries**	**Priority pathogens covered**	*Acinetobacter* spp.	*Clostridioides difficile*	*Enterobacteriaceae*	*Neisseria gonorrhoeae*	*Pseudomonas aeruginosa*	*Campylobacter* spp.	*Enterococcus faecium*	*Enterococcus* spp.	*Mycobacterium tuberculosis*	*Salmonella* spp.	*Staphylococcus aureus*	*Streptococcus pneumoniae*	*Candida* spp.	*Haemophilus influenzae type b (Hib)*	*Streptococcus* (group A)	*Streptococcus* (group B)
Antimicrobial Testing Leadership And Surveillance (ATLAS)	Pfizer	2004	81	13	●	●	●	●	●	●	●	●	○	○	●	●	○	●	●	●
CANWARD	Abbott; MSD; Pfizer	2007	1	13	●	○	●	●	●	○	●	●	○	●	●	●	●	●	●	●
SENTRY Antimicrobial Surveillance Program	Cipla; Pfizer; Shionogi	1997	57	11	●	○	●	○	●	○	●	●	○	○	●	●	●	●	●	●
Study for Monitoring Antimicrobial Resistance Trends (SMART)	MSD	2002	63	8	●	○	●	○	●	○	●	●	○	○	●	●	○	●	○	○
Study of Bacterial Resistance Kinki Region of Japan	Shionogi	1997	1	8	●	○	●	○	●	○	○	●	○	○	●	●	●	●	○	○
BSAC Bacteraemia Resistance Surveillance Programme	MSD; Pfizer	2000	2	7	○	○	●	○	●	○	○	●	○	○	●	●	○	○	●	●
Abbott Restora Infectious Diseases Scientific Excellence (ARISE)	Abbott	2019	1	5	○	○	●	○	●	○	○	○	○	○	●	○	○	○	●	●
Data Development	Viatris	2019	1	5	○	○	●	●	●	○	○	○	○	○	●	○	○	●	○	○
Surveillance of Tedizolid Activity and Resistance (STAR)	MSD	2011	14	5	○	○	○	○	○	○	●	●	○	○	●	○	○	○	●	●
National Reference Centre for the Diagnostics of Central Nervous System Bacterial Infections (KOROUN)	Novartis	2019	1	4	○	○	○	○	○	○	○	○	○	○	○	●	○	●	●	●
Shionogi Japanese surveillance studies Programme	Shionogi	1992	1	3	○	○	○	○	○	○	○	○	○	○	●	○	○	○	●	●
SIDERO-WT Programme	Shionogi	2014	13	3	●	○	●	○	●	○	○	○	○	○	○	○	○	○	○	○
Program to Assess Ceftolozane/Tazobactam Susceptibility (PACTS)	MSD	2011	29	2	○	○	●	○	●	○	○	○	○	○	○	○	○	○	○	○
Survey of Antibiotic Resistance (SOAR)	GSK	2002	43	2	○	○	○	○	○	○	○	○	○	○	○	●	○	●	○	○
Drug Resistance Emergence Assessment in MDR-TB (DREAM)	Johnson & Johnson	2015	11	1	○	○	○	○	○	○	○	○	●	○	○	○	○	○	○	○
Pretomanid Resistance Surveillance Program	Viatris	2020	8	1	○	○	○	○	○	○	○	○	●	○	○	○	○	○	○	○
Observatoires Régionaux du Pneumocoque (ORP)	Sanofi	2000	1	1	○	○	○	○	○	○	○	○	○	○	○	●	○	○	○	○
China-based antibiotic resistance surveillance programs (CHINET) / CHIFNET	Pfizer	2005	1	0	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Three Academic Societies Joint Antimicrobial Susceptibility Surveillance Program	Shionogi	2004	1	0	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●

● Applies ● Unknown ○ Does not apply

* Bacteria and fungi identified as priority R&D targets for limiting AMR, by the WHO and/or the US Centers for Disease Control and Prevention (CDC). See Appendix V. Priority bacteria and fungi that are not covered by surveillance programmes are not listed in this table. These are: *Bordetella pertussis, Helicobacter pylori*, *Salmonella non-typhoidal & serotype typhi*, *Shigella* spp., *Aspergillus fumigatus* and *Candida auris*.

SURVEILLANCE PROGRAMMES THAT STAND OUT

Programme: ATLAS
Company: Pfizer
Pathogens: 13 priority pathogens
Countries: 81
Scope: Resistance against Pfizer's antibacterial & antifungal medicines
Data-sharing: Raw data is publicly available

Pfizer expanded its ATLAS programme to include more priority pathogens and more countries through the Surveillance Partnership to Improve Data for Action on Antimicrobial Resistance (SPIDAAR), a new collaboration with the governments of Ghana, Kenya, Malawi and Uganda. Raw data (from 2018) is available for download on the AMR Register, which is an open-access data platform. Aggregated results (of antibacterial and antifungal resistance data) are shared on the ATLAS website, which is also an open-access data platform, as well as through open-access journal articles.

Priority pathogens identified by WHO and/or the CDC are known for leading to resistant infections and deaths. According to the CDC, more than 3.1 million infections caused by priority pathogens occur in the US each year, and more than 49,000 people die as a result.[4] Out of all surveillance programmes from companies in scope, ATLAS and CANWARD both cover the most priority pathogens, however ATLAS has a broader geographic scope than CANWARD.

Programme: SENTRY
Companies: Cipla; Pfizer; Shionogi
Pathogens: 11 priority pathogens
Countries: 57
Scope: Changes in resistance patterns over time, worldwide
Data-sharing: Aggregated results are publicly available

SENTRY is a multinational programme managed by JMI laboratories and supported by several companies in scope. This programme is one of three which cover *Candida* spp., a fungal pathogen which is estimated to have caused more than 34,000 hospitalisations and 1,700 deaths in the US in 2017.[5]

The managing partner, JMI laboratories, publicly shares aggregated results on the SENTRY website, as well as through open-access journal articles.

Programme: SMART
Company: MSD
Pathogens: 8 priority pathogens
Countries: 63
Scope: Respiratory, complicated intra-abdominal and urinary tract infections, and bloodstream isolates
Data-sharing: Aggregated results are publicly available

One of the priority pathogens covered by SMART is *S. pneumoniae*, which causes pneumococcal disease, ranging from ear and sinus infections to pneumonia and bloodstream infections. *S. pneumoniae* is estimated to have caused 900,000 infections and 3,600 deaths in the US in 2014.[5]

MSD shares the aggregates results in open-access journal articles, as well as on the online SMART database, which is restricted and cannot be accessed without registration.

Programme: CANWARD
Companies: Abbott; MSD; Pfizer
Pathogens: 13 priority pathogens
Countries: Canada
Scope: Pathogens isolated in Canadian hospitals
Data-sharing: Aggregated results are publicly shared

CANWARD is a national programme focused on 13 priority pathogens. In Canada, it was estimated that resistant infections contributed to 14,000 deaths in 2018.[6]

The managing partner, the Canadian Antimicrobial Resistance Alliance, shares aggregated results of the CANWARD programme on an open-access data platform, as well as through open-access journal articles.

STEWARDSHIP– SURVEILLANCE

Slow progress and varied strategies for data sharing

Making surveillance results – and, most importantly, raw data – publicly available is key to helping governments, public health authorities and healthcare professionals (HCPs) measure and respond to the spread of resistant infections, analyse local trends and prioritise objectives in stewardship policies. The Benchmark looks for companies to share raw data so that the WHO, third-party researchers and other experts have the information needed for further research, beyond the specific questions asked by the companies themselves.

The Benchmark notes that companies are using different mechanisms to make surveillance data available. For example, Johnson & Johnson is sharing data from clinical trials in the YODA platform which can only be accessed via approval through an independent scientific committee, while MSD is reportedly preparing to host its raw data on its website, with a process for researchers to request access. However, data shared in a restricted manner has limited use as it is not freely available to public health bodies, which may not be able to predict which analyses might be needed in the future. Furthermore, such data has a public health importance and should therefore not be withheld.

Although GSK and Shionogi have both pledged to share raw surveillance data publicly, there is no progress to report at the time of writing. Novartis and Sanofi have started sharing surveillance data since the previous Benchmark report in 2020, having published aggregated results of their surveillance studies in open-access journal articles. Pfizer remains the only company in scope to reach the gold standard by publicly sharing its raw data. It shares raw data from its ATLAS programme (from 2018) on the AMR Register, an open-access data platform.

How governments and industry can work together

AMR surveillance is a largely neglected branch of public health. While the Benchmark recognises that action from pharmaceutical companies is needed, this can be achieved more effectively if countries are also active in setting up surveillance systems, identifying gaps and setting guidelines to harmonise the data.

Transparency in sharing surveillance data is beneficial to public health authorities as it can help healthcare professionals to make informed treatment choices, forecast disease trends, and plan medicine purchases. It can also be used to inform policy directives and investment decisions, including diagnostic laboratory capacity and infection prevention and control responses, or identifying new emerging pathogens. It is important that all stakeholders work collaboratively and in solidarity to coordinate and scale up AMR surveillance.

FIGURE 63. **Surveillance programmes share data in different ways**

This figure shows the data-sharing practices of the 19 surveillance programmes in which the 10 companies take part. The majority of programmes publish their results in an aggregated form. Only one programme shares raw data via an open-access platform.

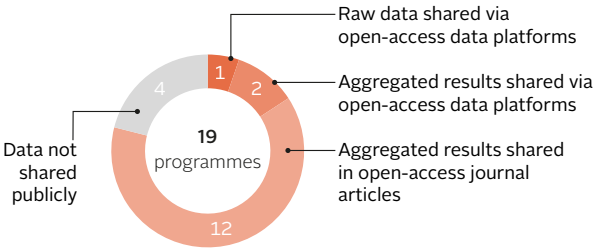


FIGURE 64. **Best practice: AMR surveillance data sharing**

BEST PRACTICE

1 company publishes aggregated results via data platforms in a restricted manner	6 companies publish aggregated results via open-access journal articles	4 companies publish aggregated results via open-access data platforms	1 company publishes clinical trial raw data via data platforms in a restricted manner	1 company publishes raw data via open-access data platforms
Abbott	GSK MSD Novartis Pfizer Sanofi Shionogi	Abbott MSD Pfizer Shionogi	Johnson & Johnson	Pfizer

STEWARDSHIP– SALES PRACTICES

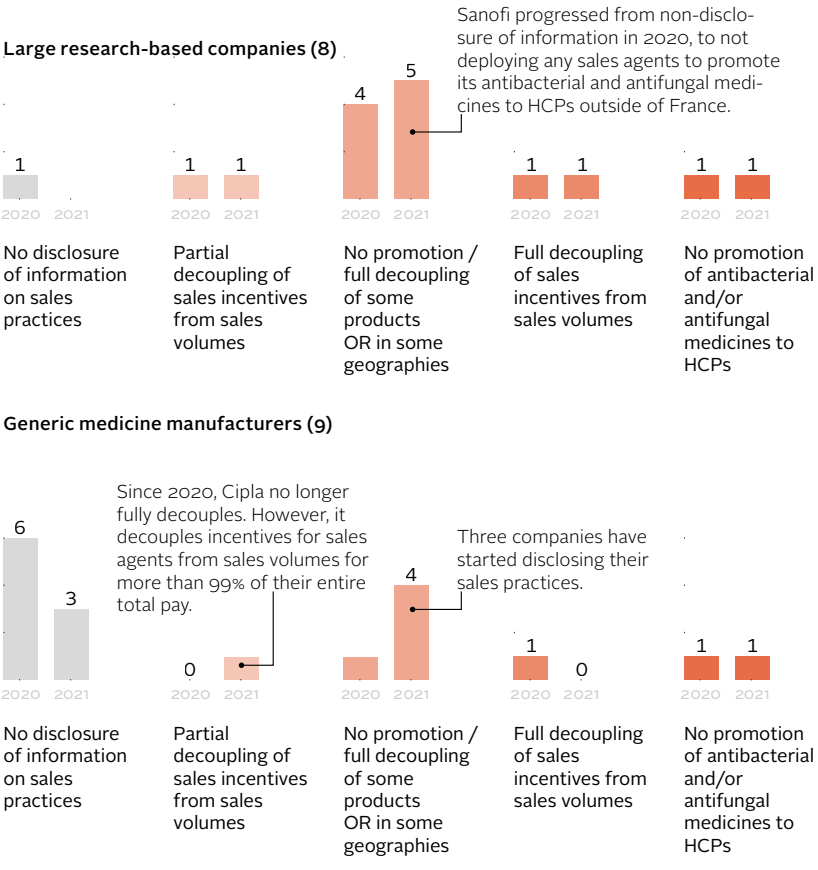
Overall progress in sales practices, especially among generic medicine manufacturers

When sales agents' bonuses are linked to how much antibacterial and antifungal medicine is sold, this acts as an incentive for these staff to oversell in order to increase their own pay. Companies can minimise the risk of overselling by removing the link between sales volume and financial rewards, or – going further – by stopping the use of sales agents for antibacterial and antifungal medicines altogether.

In 2020, the Benchmark reported progress in this area, namely a jump from five companies to ten companies that stopped the use of sales agents altogether, or are decoupling bonuses from sales volume of antibacterial and antifungal medicines.

In 2021, data shows that more generic medicine manufacturers are taking action to combat overselling with three additional companies putting policies in place, namely Abbott, Aurobindo and Viatris. Moreover, among the large research-based companies, Sanofi updated its policies around promotion of its antibacterial and antifungal medicines outside of its home country, France. However, progress in improving sales practices is not always consistent, and company behaviour around promotion can quickly change, so complacency should be avoided.

FIGURE 65. **How far do companies go in decoupling performance incentives from sales volumes?**
The charts show how many of the 17 companies in scope are addressing this issue, compared with how they performed in the 2020 Benchmark.



KEY TERMS

Decoupling incentives from sales
Full decoupling means that no component of a sales agent's incentives is linked to that agent's volume of sales. Partial decoupling means that a proportion of the agent's pay is variable and depends on incentives linked to sales volumes.

Percentage of variable pay
Variable pay can be linked to performance targets (related to behaviour or education) or sales volumes. The higher the percentage of variable pay linked to sales volumes, the more incentive there is to increase sales volumes.

Level of incentives
Incentives for sales agents can be awarded at individual, smaller group or national level. When incentives are awarded at national and smaller group (rather than individual) level, they are linked less directly to total pay, so that when an individual agent sells a higher volume of products, this does not directly increase that person's total pay.

DIFFERENCES BETWEEN COMPANIES

Large research-based companies and generic medicine manufacturers operate in different ways, which can have an impact on sales and promotional practices.

- **Large research-based companies** mostly focus on developing new, innovative medicines. These are typically promoted after receiving market approval because they still need to be implemented in daily medical practice, treatment guidelines or medical formularies.
- **Generic medicine manufacturers** are focused on producing and manufacturing generic medicines that are launched after the patent on innovative medicines has expired, with the exception of when production of an on-patent product is licensed to that manufacturer. Generic medicines, with the exception of branded generics, are typically not promoted on a product level as the product is already implemented in daily practice. However, generic medicine manufacturers usually compete in government or hospital tenders to sell generic medicines.

Which companies are decoupling financial incentives from sales volumes?

Teva, Aurobindo and Shionogi go the furthest towards ensuring that sales agents' financial incentives are not tied to sales volume, either by not promoting their products or by fully decoupling such incentives. Johnson & Johnson, Otsuka and Viatris do not promote their tuberculosis medicines, with the exception of Johnson & Johnson, which promotes its multidrug-resistant TB medicine bedaquiline (Sirturo®) in at least one country.

Abbott, Aurobindo, Sanofi and Viatris have newly taken steps in this area. A range of strategies are being implemented, for example pilots for full decoupling, or no promotion in some countries and/or for some products. However, the true impact of these pilots remains unknown. Further progress is still needed toward full decoupling, or towards a policy of no promotion to healthcare professionals globally.

Progress on sales practices has proven to be inconsistent throughout the Benchmark iterations as GSK regressed in this area in the 2020 Benchmark, but the group of companies as a whole has progressed as more generic medicine manufacturers are starting to get more involved in this area.

TABLE 9. **Overview of sales practices, broken down by company and by coverage of products and geographies**

This table shows which measures each company is taking – or not taking – to decouple financial incentives from sales volume for their sales staff.

	Portfolio size*	No promotion to healthcare professionals		Full decoupling of sales incentives from sales volumes		Partial decoupling of sales incentives from sales volumes	
		Products	Geographies	Products	Geographies	Level of sales targets	% of pay decoupled from volumes
		● Applies to all ● Applies to some ○ Applies to none				● National ● Smaller group ● Individual ● Unknown ● Confidential	
Large research-based pharmaceutical companies							
Pfizer	112	○	○	●	●	●	●
Novartis	109	○	○	○	○	●	72%
Sanofi	40	●	●	○	○	●	●
GSK	34	○	○	○	○	●	75%
MSD	15	○	○	●	●	●	●
Johnson & Johnson	9	●	●	○	○	●	●
Shionogi	9	○	○	●	●	N/A	N/A
Otsuka	1	●	●	N/A	N/A	N/A	N/A
Generic medicine manufacturers							
Teva	143	●	●	N/A	N/A	N/A	N/A
Abbott	87	○	○	●	●	●	●
Viatris	87	●	●	○	○	●	●
Cipla	69	○	○	○	○	●	>99%
Alkem**	52	○	○	○	○	●	●
Fresenius Kabi	52	○	○	○	○	●	●
Sun Pharma**	52	○	○	○	○	●	●
Hainan Hailing**	43	○	○	○	○	●	●
Aurobindo	37	●	●	N/A	N/A	N/A	N/A

Shionogi has been consistent in its approach to sales practices since 2017.

Teva has the largest portfolio size of any company in scope, and has been consistent since the 2020 Benchmark in its policy of not deploying sales agents for the sales of its antibacterial and antifungal medicines globally.

Abbott ran a pilot in 2021 where it fully decoupled incentives for sales agents from sales volumes of an anti-infective in India for three months.

Viatris does not deploy any sales agents to promote pretomanid or flucytosine to HCPs.

Aurobindo does not deploy sales agents for the sales of its antibacterial and antifungal medicines globally.

* Antibacterial and/or antifungal medicines.

** Alkem, Sun Pharma and Hainan Hailing do not disclose their sales practices.

Reimbursement schemes could help companies make progress

There are gaps in standards on advertising, marketing and sales of antimicrobials, but there are also new approaches being used which could lead to improvements.[7] These include the use of reimbursement schemes, which aim to remove the component of sales volumes entirely.

As part of pilot schemes ongoing in the UK and Sweden,[8] promising new antibacterial medicines that are about to reach the market are selected, and the schemes ensure that reimbursement by the government is not related to the volume of medicines sold or used. This aligns with stewardship practices, as new antibacterial medicines should be used sparingly and only as a last resort to avoid the emergence of resistance against the newest antibacterial medicines on the market.

These new reimbursement schemes provide an opportunity for pharmaceutical companies to completely break the link between sales volumes and financial incentives, while still retaining an appropriate revenue. Going forward, this could be an especially helpful model to apply to low- and middle-income countries.

STEWARDSHIP– COI MITIGATION

Conflict of interest comprehensively mitigated in education programmes for healthcare professionals

Pharmaceutical companies know how their medicines can be used, responsibly and appropriately, to treat different infections. Many pharma companies contribute to educational activities for healthcare professionals (HCPs) on how best to manage the risk of resistance while using their products; but if they do so, they must proactively avoid the risks of conflicts of interest (COI) which are inherent in this area.

Looking at a maximum of five programmes per company, the Benchmark assesses whether and how companies engage in educational activities aimed at HCPs, and whether they mitigate COI as part of those programmes.

In 2020, the Benchmark reported that the majority of programmes evaluated had comprehensive measures in place to mitigate the risk of COI in their educational programmes targeting HCPs. In 2021, there is further progress, as all programmes have at least some COI mitigation in place and there is an increase in the number of programmes with comprehensive COI mitigation. The maximum of five programmes per company which are included in this analysis demonstrate a high exemplary standard of COI mitigation; companies must further ensure that this standard applies to all of their programmes.

As in 2020, programmes are most likely to be developed in-house and thus supported by one or more of the three COI mitigation strategies defined by the Benchmark. The most common strategy is a pledge not to give any financial and material incentives to participants in the programme.

FIGURE 66. **Levels of COI mitigation among the educational programmes assessed by the Benchmark**

The Benchmark assessed 57 educational programmes across the companies in scope. This figure shows how comprehensive the COI mitigation is, and also highlights which companies are involved in the programmes which do not have comprehensive COI mitigation in place.

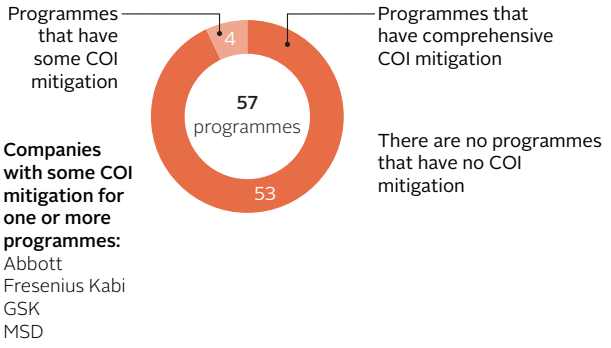
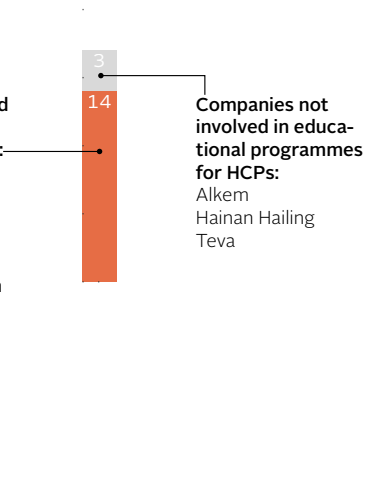


FIGURE 67. **How many companies report that they are involved with HCP education?**

This figure shows which companies are involved in AMR-related education for HCPs.



How companies can mitigate conflict of interest in educational programmes for healthcare professionals

No incentives to participants: A company pledges that it will not provide financial and material incentives to those who participate in educational programmes.

Independence of content development: The exclusion of a company's marketing department in content development and speaker selection.

No branded materials: The content of an educational programme excludes branded products or materials.

Unrestricted grant: Companies can provide unrestricted grants to independent third parties. These can be used for AMR-related educational activities, without any involvement of the company and without any obligation to include marketing aspects in the programme.

Independent review: An independent review is the most robust way for companies to show they mitigate COI within programmes. An independent body such as the Accreditation Council for Continuing Medical Education (ACCME) can evaluate how COI is mitigated if the provider is a company, and can accredit educational programmes.

FIGURE 68. **The number of educational programmes using different COI mitigation strategies**

All 57 programmes in scope are covered by at least one COI mitigation strategy. This figure shows how many programmes use the different types of mitigation strategies, defined on the left.

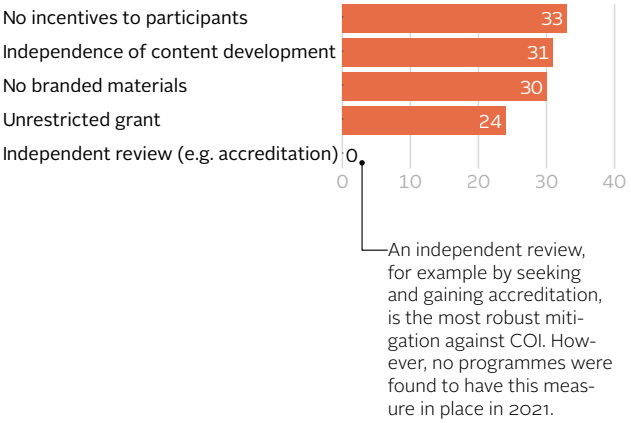


TABLE 10. **Which COI mitigation strategies are used in HCP educational programmes?**

This figure shows which COI mitigation strategies are used by companies for their HCP educational programmes, broken down by whether they are delivered by an independent third party or in-house.

		Third party		In-house		
	Number of programmes*	Unrestricted grant	Independent review / accreditation	Independence of content development	No incentives to participants	No branded materials
Abbott	5	●	○	●	●	◔
Cipla	5	○	○	●	●	●
Fresenius Kabi	5	○	○	◔	●	●
GSK	5	○	○	●	●	◔
Johnson & Johnson	5	●	○	○	○	○
MSD	5	●	○	◔	●	◔
Novartis	5	●	○	●	●	●
Pfizer	5	●	○	○	○	○
Shionogi	5	●	○	●	●	●
Sun Pharma	5	●	○	○	○	○
Viatris	5	●	○	●	●	●
Aurobindo	1	○	○	●	●	●
Otsuka	1	○	○	●	●	●
Sanofi	1	○	○	●	●	●
Alkem**	0	◌	◌	◌	◌	◌
Hainan Hailing**	0	◌	◌	◌	◌	◌
Teva**	0	◌	◌	◌	◌	◌

● Applies to all programmes
◔ Applies to some programmes
○ Applies to no programme
◌ Not applicable

* Up to five programmes in total are evaluated for each company.

** If the company is not involved in AMR-related educational programmes for healthcare professionals, there is no conflict of interest mitigation to be assessed.

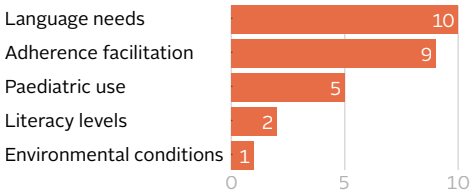
STEWARDSHIP – ADHERENCE

Companies support appropriate use through brochure and packaging adaptations

The risk of resistance is lowered when patients understand the risks and adhere to their courses of treatment until they are completed. When patients are prescribed medicines, the packaging as well as materials such as informational brochures can help them to understand AMR, and how they can minimise these risks to themselves and their communities. Pharmaceutical companies can adapt packaging materials to ensure information is clear, for example by presenting it in a local language, or by supporting it by pictograms in areas with low levels of literacy.

Eleven companies out of 17 report taking steps to minimise AMR and facilitate appropriate use through brochure and packaging adaptations. Since the last Benchmark, Abbott and Aurobindo now report making adaptations.

FIGURE 69. **Which types of adaptations do companies use?**
This graph shows how many times each different type of brochure or packaging adaptation is reported as being used by any of the companies in scope, for any of their products in scope.



Issues that can prevent appropriate use by patients	Examples of how companies adapt their product brochures or packaging to help improve appropriate use
Language needs Patients may not be able to read the included instructions on how to use the product appropriately if they are not written in the local language.	**Eight companies have made language adaptations** • Cipla adapted its patient education leaflets for itraconazole, oxiconazole and fosfomycin trometamol in India. These leaflets contain QR codes that redirect to information in eight to ten regional languages in India: Assamese, Bengali, Gujarati, Kannada, Malayalam, Marathi, Odia, Punjabi, Tamil, and Telugu. • Teva's packaging for azithromycin and linezolid contains information that is translated into English, Spanish, French and Portuguese. The multilingual packaging was adapted for the receiving country.
Adherence facilitation Patients may not be aware they need to finish the full course of treatment even if they start feeling better.	**Six companies have made adaptations to facilitate adherence** • Cipla created leaflets for itraconazole and amorolfine that contain information about things to be considered while taking antifungal medication, e.g. to complete the course of treatment even if symptoms improve earlier. • Johnson & Johnson packaged a six-month treatment regimen (188 tablets) of bedaquiline (Sirturo®) in a single bottle. This was designed to enable patients to follow a full course of treatment without needing to make multiple visits to a pharmacy or clinic.
Paediatric use For paediatric patients there may be different requirements for the administration or dosing of the product.	**Five companies have made adaptations for paediatric use** • Abbott adapts packaging of eight antibacterial paediatric suspensions by including a QR code on the packaging that directs to a video explaining how to use them appropriately. • Pfizer has adapted packaging of azithromycin (Zithromax®) as an oral suspension to include a QR code that directs patients to a video explaining how to administer the oral suspension properly for adults and children. This is applied in Vietnam and the Philippines and the video is played in the local language.
Literacy levels For illiterate patients it is difficult to understand written instructions on how to use the product appropriately.	**Two companies have made literacy-related adaptations** • Abbott adapts packaging for antibacterial medicines in India by including pictograms to illustrate the recommended usage regimen.
Environmental conditions Local environmental conditions can decrease the effectiveness of the product.	**One company has made an environmental adaptation** • GSK designed blister packaging for amoxicillin/clavulanic acid (Augmentin™) with a specific lidding foil that is sensitive to moisture ingress for high humidity environments. This technology also received the Alufoil Trophy Award for its innovation in technical packaging.

More than half of companies support patient education on the risks of AMR

Ten companies are involved in general patient education on AMR through awareness campaigns, brochures, posters, articles, videos, games, comic booklets and a TV drama series.

TABLE 11. **How do companies help patients understand the risks of AMR?**

Company	Name of initiative	Description of initiative	Examples of initiative	
Novartis	Mejor Cuidado, Más Salud	Novartis created an educational and emotionally-driven multichannel campaign targeted at parents of children: "Better Care More Health" or "Mejor Cuidado, Más Salud". This campaign includes an extensive outreach (including a website, videos, email campaign, presentation, brochures and posters) during World Antibiotic Awareness Week in November.		
Johnson & Johnson	MTV Nishedh Live (TV drama series)	Johnson & Johnson funds the MTV Staying Alive Foundation, which created a TV drama series that includes a storyline about young people with TB to help inform them about the signs and symptoms of the disease and to help reduce the social stigma often faced by patients.		
Sanofi	AnTRIbiotics; Bact' Attack; Antibio-Responsable	Sanofi educates patients through the AnTRIbiotics campaign with Cyclamed (in France), a game application called Bact' Attack, a comic booklet on adherence to tuberculosis treatment (in South Africa) and a website (in French) about the responsible use of antibiotics.		

STEWARDSHIP

Looking ahead

Antimicrobial stewardship has been a casualty of the COVID-19 pandemic as stewardship programmes were disrupted by changes in healthcare delivery, consequently leading to the over-prescription of broad-spectrum antimicrobials for COVID-19 patients – despite low evidence of bacterial/fungal co-infection.[9,10] While this highlights the scale of the challenge in antimicrobial stewardship, there are clear ways in which different stakeholders can help tackle the problem.

COMPANIES

AMR surveillance

- Engage in AMR surveillance programmes to track antimicrobial resistance, either by setting up programmes in-house or by funding external programmes run by institutions such as research organisations.
- Publicly share raw data from these programmes in a readily accessible manner.

Sales practices

- Fully and consistently decouple incentives for sales agents from sales volumes, either by avoiding the use of sales agents altogether for antibacterial and antifungal medicines, or by removing the financial incentive linked to sales volumes of these medicines.

COI mitigation in education programmes

- Ensure a robust conflict of interest (COI) mitigation strategy when the company is engaged in educational stewardship activities directed at healthcare professionals.
- Adopt the most effective strategies by either funding an independent third party to develop programmes, or seeking accreditation for in-house programmes.

Adherence

- Adapt brochures and packaging of antibacterial and antifungal medicines to facilitate appropriate use by patients.
- Consider the needs of the patient population, such as local languages, literacy levels and paediatric use.

INVESTORS

- Consider whether companies are taking stewardship into account for their antibacterial and antifungal medicines.
- Specifically focus on companies' engagement in responsible promotional and sales practices and AMR surveillance.

GOVERNMENTS AND PROCURERS

- Set up surveillance systems, identify gaps in AMR surveillance data, and set up guidelines to harmonise the different types of surveillance data.
- Continue setting up reimbursement schemes for new antibacterial and antifungal medicines in which reimbursement is not related to the volume of medicines sold. This can help remove the financial incentive linked to sales volume for pharmaceutical sales agents, while retaining an appropriate revenue for the companies.
- Enforce responsible promotional practices, for example regarding ethical codes and financial or material incentives for healthcare professionals.
- Educate healthcare professionals on the risks of AMR and new treatment guidelines. This is a responsibility for governments, not pharmaceutical companies, so if healthcare professionals are already fully up-to-date on AMR education then there is no need for companies to get involved in this area.

ACADEMIA / RESEARCH

- Pave the path for governments, public health authorities, healthcare professionals and other researchers to utilise raw data from AMR surveillance. For example, this can be used to forecast disease trends; plan medicine purchases; make better-informed treatment choices; improve policy directives and investment decisions for laboratory capacity, infection prevention and control response; and identify newly emerging pathogens.
- Share knowledge of AMR and up-to-date treatment guidelines and recommendations for healthcare professionals that are independent from educational activities from pharmaceutical companies.
- Perform studies about systematic medicine use in order to create a baseline, identify key problems for corrective action, and measure follow-up.
- Evaluate the impact of AMR education for healthcare professionals and further optimise the practices, policies, and programmes to improve prescribing behaviour and/or to set up the appropriate facilities and structures to support.

REFERENCES

1. Van Boeckel TP, Gandra S, Ashok A, et al. Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. Lancet Infect Dis. 2014;14(8). doi:10.1016/S1473-3099(14)70780-7

2. World Health Organization. Global Antimicrobial Resistance and Use Surveillance System (GLASS) Report.; 2014.

3. World Health Organization. National Action Plan of the Islamic Republic of Iran for Combating Antimicrobial Resistance(IRIAMR) 2016 - 2021.; 2016. https://www.who.int/publications/m/item/iran-national-action-plan-of-the-islamic-republic-of-iran-for-combating-antimicrobial-resistance. Accessed August 31, 2021.

4. Africa CWJ, Abrantes PM dos S. Candida antifungal drug resistance in sub-Saharan African populations: A systematic review. F1000Research. 2017;5. doi:10.12688/f1000research.10327.1

5. Centers for Disease Control and Prevention. Biggest Threats and Data.; 2019. https://www.cdc.gov/drugresistance/biggest-threats.html. Accessed August 5, 2021.

6. The Expert Panel on the Potential Socio-Economic Impacts of Antimicrobial Resistance in Canada. When Antibiotics Fail.; 2019. https://cca-reports.ca/reports/the-potential-socio-economic-impacts-of-antimicrobial-resistance-in-canada/. Accessed September 1, 2021.

7. Van der Heijden M. Strengthening the regulation of antimicrobial use to mitigate drug resistance. Global Antibiotic Research and Development Partnership (GARDP). https://revive.gardp.org/strengthening-the-regulation-of-antimicrobial-use-to-mitigate-drug-resistance/. Published July 16, 2021. Accessed August 31, 2021.

8. Gotham D, Moja L, van der Heijden M, Paulin S, Smith I, Beyer P. Reimbursement models to tackle market failures for antimicrobials: Approaches taken in France, Germany, Sweden, the United Kingdom, and the United States. Health Policy (New York). 2021;125(3). doi:10.1016/j.healthpol.2020.11.015

9. Lynch C, Mahida N, Gray J. Antimicrobial stewardship: a COVID casualty? J Hosp Infect. 2020;106(3):401-403. doi:10.1016/j.jhin.2020.10.002

10. Rawson TM, Moore LSP, Zhu N, et al. Bacterial and Fungal Coinfection in Individuals with Coronavirus: A Rapid Review to Support COVID-19 Antimicrobial Prescribing. Clin Infect Dis. 2020;71(9):2459-2468. doi:10.1093/cid/ciaa530

2021 Antimicrobial Resistance Benchmark

Best Practices

RESEARCH AND DEVELOPMENT: BEST PRACTICE 1

GSK maintains lead in antibacterial and antifungal R&D to target priority pathogens

GSK
Topic: Size of R&D pipeline targeting priority pathogens
What: GSK has the largest R&D pipeline of projects targeting pathogens in scope across all companies
Region: Global

As antimicrobial resistance spreads, new medicines and vaccines that target priority bacterial and fungal pathogens are needed urgently. Infectious diseases projects are risky for companies due to the scientific challenges of discovering new antibiotics, the complexities of development and the limited economic attractiveness of the market.

The Benchmark expects large research-based pharmaceutical companies to continue engaging and investing in R&D that targets priority bacterial and fungal pathogens. Especially urgent is the need to develop products that offer a better chance of lasting effectiveness by operating in novel ways. To determine how 'novel' a medicine or vaccine is, the Benchmark uses four criteria defined by the World Health Organization (these are: new chemical class; new target; new mode of action; and/or absence of cross-resistance).

Why does GSK lead in R&D?

Of the eight large research-based pharmaceutical companies evaluated, GSK invests the largest absolute amount in R&D. It leads in R&D targeting the priority bacteria and fungi in scope, with a total of 31 projects in the pipeline (up from 27 in 2020), more than half (19) are in discovery and preclinical stages. Of all companies in scope, GSK's pipeline is the biggest, addresses more pathogens designated as 'critical' and/or 'urgent' threats (by the WHO and/or US Centers for Disease Control) than others, has the most vaccines projects, and is developing the largest number of innovative treatments. By investing in innovation and with a high proportion of projects at an earlier (riskier) stage, GSK shows best practice.

Six of eight companies in scope for the R&D Research Area are developing candidates that target pathogens in the 'critical' and/or 'urgent' threat categories, including 18 that are in clinical-stage development or are recently approved products. GSK has the most of these projects, followed by Pfizer and Shionogi. Since 2020, these companies have increased their number of 'critical' and/or 'urgent' priority pathogen projects.

GSK is developing gepotidacin, a late-stage candidate that is considered a new chemical class, with a new mechanism of action, which targets *E. coli* and *N. gonorrhoeae*. The latter is a pathogen that experts warn could become resistant to all currently available antibiotics. The company also has an anti-tuberculosis agent considered a new chemical class, with a new target, new mode of action and no known cross-resistance to other antibacterial classes.

Reflecting its commitment to prevent infections and reduce society's dependence on antibiotics, GSK dedicates more than half of its R&D pipeline to vaccine projects. Of the six companies active in vaccine R&D, GSK reports by far the most projects (16), 13 of which are innovative and three that are adaptive. Both GSK and Pfizer (with the second highest number of vaccine projects) have candidates in clinical development to prevent *C. difficile*, one of the most common causes of hospital-acquired infections, with an increasing incidence worldwide.

NEXT STEPS

Since 2018, the Benchmark has recognised GSK as being at the forefront of antimicrobial R&D. The company supports the AMR Action Fund along with six other companies assessed by the Benchmark (Johnson & Johnson, MSD, Novartis, Pfizer, Shionogi and Teva), and it collaborates on a diverse range of projects with partners and funders including the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), the Bill & Melinda Gates Medical Research Institute, the TB Alliance, Wellcome Trust and the National Institutes of Health (NIH).

In the last 20 years, investment in innovation for antibacterial medicines and vaccines has declined. The Benchmark expects all large research-based pharmaceutical companies to continue to engage and invest in R&D to combat the spread of AMR, whether through private funding or by joining consortia with public funding, and/or through discovery programmes, in-licensing or acquisitions. Companies must find new ways to develop and commercialise novel products that can remain effective, and ensure they reach the populations that need them.

RESEARCH AND DEVELOPMENT: BEST PRACTICE 2

Pfizer makes strategic investment in antibacterial and antifungal R&D to get new products to market

PFIZER

Topic: R&D pipeline targeting priority pathogens
What: Pfizer has developed a diverse strategy to maintain and evolve its engagement in R&D, and actively seeks new opportunities to expand and enrich its involvement
Region: Global

New medicines and vaccines are needed urgently to target priority pathogens. However, it can be risky to invest in developing antibacterial and antifungal products. Large companies that possess greater capacity, scientific expertise, equipment and regulatory know-how can play a valuable role when they choose to invest in smaller companies, and/or acquire promising innovations. This can help to take forward products at a greater speed.

What does best practice look like?

Pfizer works internally and externally to maintain and grow its engagement with AMR, focusing both on treatment and on the prevention of infections caused by difficult-to-treat resistant pathogens. In contrast with GSK, a high proportion of its R&D projects (eight of 13) are in late-stage clinical development (Phase II and onwards).

Pfizer's diverse strategy includes acquiring innovation from others, supporting smaller biotech companies, and increasing its in-house pipeline. It engages across all sectors to support R&D and works with a range of private and public partners and funders including the US government (BARDA), AbbVie and the Bill & Melinda Gates Foundation. It also supports the AMR Action Fund, pledging USD 100 million over 10 years.

By putting its weight behind innovative, early-stage R&D, the company is helping to bring promising novel products to market. Strategic acquisitions such as Arixa Pharmaceuticals and Amplyx Pharmaceuticals have helped grow Pfizer's pipeline of projects from eight to 13 and broaden the number of pathogens targeted. Through Amplyx, Pfizer moved into antifungal R&D and is now developing a clinical-stage antifungal medicine candidate (fosmanogepix) to treat invasive fungal infections caused by *Candida* spp. among others. Through Arixa's lead compound ARX-1796, Pfizer aims to create next-generation oral antibiotics, targeting gram-negative pathogens that cause resistant urinary tract and other infections. In late 2019, Pfizer also invested in ContraFect, which is taking forward Phase III trials of its candidate exebacase, a first-in-class direct lytic agent targeting *S. aureus*, to help patients with highly resistant infections.

Pfizer's vaccine development programme is second in size only to GSK's and has products to help protect against Group B *Streptococcus* and respiratory syncytial virus. Its vaccine for *S. pneumoniae* was recently approved by the FDA. Its *C. difficile* vaccine is in Phase III trials, ahead of GSK's own *C. difficile* candidate.

NEXT STEPS

The Benchmark expects large research-based pharmaceutical companies to continue engaging and investing in R&D that targets priority bacterial and fungal pathogens, whether in-house or through collaborations. Pfizer engages with AMR from a range of angles and liaises with diverse stakeholders and local networks in low- and middle-income countries. In R&D, its approach is highly strategic: it identifies promising candidates for investment and supports smaller innovators to move products forward to market. Other companies can emulate this proactive, strategic approach and their ongoing commitment to AMR.

RESEARCH AND DEVELOPMENT: BEST PRACTICE 3

Otsuka and Pfizer set consistent standard for stewardship and access plans

OTSUKA, PFIZER, GSK, SHIONOGI, SANOFI
Topic: Stewardship and access planning during late-stage development
What: Comprehensive plans for late-stage projects, with a variety of strategies tailored to the product being developed
Region: Global

Antimicrobial resistance poses opposing challenges: access and excess. Millions of people live without reliable access to effective antibacterial and antifungal products, yet excessive or inappropriate use of these products can render them ineffective. The need to enhance access goes hand in hand with that of ensuring appropriate use to keep medicines working.

When companies plan for these challenges during R&D, they take account of public health needs and can ensure more rapid access to new medicines and vaccines at more affordable prices following their entry to markets. Companies are expected to have plans in place for pipeline projects in Phase II and beyond. The Benchmark assesses the extent to which companies create and disclose plans to make new products swiftly accessible upon market entry, and to ensure they are used appropriately thereafter. For medicines, plans for access must be coupled with plans for stewardship.

Specifically, the Benchmark looks at the late-stage antibacterial and antifungal R&D projects targeting priority pathogens for which companies have plans in place for access (in countries in scope and where burden of disease is higher) and for stewardship on a global basis.

Otsuka and Pfizer lead

All but two of 20 medicine projects in late-stage clinical development (from all companies in scope) have in place both an access and stewardship plan. Otsuka and Pfizer stand out, both reporting comprehensive access and stewardship plans for all late-stage projects in their pipelines. Access strategies include WHO prequalification, managed access programmes, equitable pricing, provisions for sustainable manufacturing and supply, registration, responsible IP and licensing and other provisions, some stipulated in partner agreements with organisations such as the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) and the Bill & Melinda Gates Foundation.

Otsuka has plans for two late-stage candidates, both to combat tuberculosis. For its version of delamanid to treat children with drug-resistant TB, it works with the Pediatric Drug Resistant-TB Initiative launched by the Stop TB Partnership's Global Drug Facility (GDF), national TB programmes and other stakeholders to ensure global access; it plans to complete a technology transfer shortly after receiving the first stringent regulatory authority approval of this child-friendly formulation. Otsuka is developing its second candidate (OPC-167832), a highly innovative agent in Phase II of clinical development, in partnership with the Bill & Melinda Gates Foundation, and aligns its access and stewardship plans with that foundation's global access requirements.

Pfizer does not enforce its patents in Least Developed Countries (from May 2020). It has comprehensive access and stewardship plans for most candidates, including one in Phase III (aztreonam/avibactam) to treat serious gram-negative bacterial infections in adults, for which it plans a global pre-registration compassionate use programme. It also has robust, multifaceted plans for its vaccines to prevent *C. difficile* (for which no vaccine is yet on the market) and Group B *Streptococcus* (which causes around 90,000 infant deaths annually, co-funded by the Bill & Melinda Gates Foundation).

GSK, Shionogi and Sanofi: examples of good practice

GSK deploys company-wide policies to ensure access and stewardship plans are in place for its five late-stage projects, but it does not tailor plans to specific products as much as Pfizer and Otsuka do for theirs. Shionogi has progressed by actively seeking out partners to improve access and stewardship to its antibiotic candidate (cefiderocol).

Sanofi has developed Shan6™ vaccine specifically for children in low- and middle-income countries. Shan6™ was approved in May 2021 in India. There, Sanofi has a dedicated manufacturing facility where it applies supply-chain best practices including buffer and safety stocks. Additional countries in scope for registration include Thailand and Kenya. For Shan6™, Sanofi applied for WHO prequalification to ensure access to the vaccine in all countries eligible for support from Gavi, the Vaccine Alliance. Pooled demand through UNICEF and Gavi tenders ensures quality of supply and affordability. In addition, Sanofi has developed equitable pricing strategies, conducted a payer pricing survey in nine countries, and takes account of affordability by market type.

NEXT STEPS

When pharmaceutical companies work with funders such as Wellcome Trust, the Bill & Melinda Gates Foundation or CARB-X, provisions attached to funding may require them to put in place strong access and stewardship plans. Some companies go the extra mile and develop their own plans internally. Pfizer leads the field, matching the quality of its internally developed plans with that of those it develops for co-funded projects.

RESPONSIBLE MANUFACTURING: BEST PRACTICE 1

Shionogi is first to publish the details of its antibacterial waste-management performance

SHIONOGI

Topic: Disclosure of environmental risk-management
What: Shionogi is the first company to report publicly on how it manages the environmental risk of its antibacterial waste, disclosing detailed information
Region: Japan and India

During pharmaceutical manufacturing, antibacterial residue is released into the environment through factory wastewaters. The environment, composed of water and soil, naturally contains bacteria, but when exposed to antibacterial waste that is released by the manufacturing sites, this can trigger the emergence and/or selection of resistance genes and contribute to AMR development.

Currently there are no specific regulations governing discharge of antibacterial waste, so it is important for companies to disclose publicly how they manage this. As stakeholders, such as governments, academic experts and procurers, depend on self-reporting, this increases companies' responsibility to be transparent. When companies publish details and outcomes of strategies to manage the environmental risks associated with discharge, independent third parties can analyse processes and performance, and assess progress for keeping emissions at safe levels. The publication of methods and data also allows procurers a path to ensure they can leverage responsible environmental practices of company's manufacturing in its sustainable procurement policies.

Of the 17 companies in scope, only three provide some information publicly about which sites comply with guidance on safe levels. The extent to which manufacturing practices of other companies pose a risk for AMR is not yet clear.

Why does Shionogi stand out?

As the first company to publish extensive detail, Shionogi leads the field. In 2020 it published an environmental report disclosing information on audit results covering wastewater management, solid-waste management and discharge limits. Its disclosure covers all antibacterial APIs and/or drug products the company makes at its site in Kanegasaki, Japan, and those made at nine supplier sites. Information is presented clearly and concisely, is broadly accessible and includes a table of antibacterials, as well as their connection to Shionogi sites and suppliers, and compliance with discharge limits.

At its own site, Shionogi complies with limits for all APIs and all five of its drug products. It names the locations of five out of nine supplier sites (four in Japan, one in India) and the products they supply. These quantify their discharge levels, and three of them (making flomoxef, doripenem and sulfamethoxazole/trimethoprim) comply with limits. Shionogi also names its only external private waste-treatment plant, used for disposal by incineration, in scope.

Shionogi belongs to the AMR Industry Alliance, which publishes recommended discharge limits, and it makes AMR central to its contribution to global sustainability. By self-regulating and sharing information proactively (so far, only 33% of its supplier sites fully comply with guidance), the company sets a precedent for transparency. It demonstrates best practice by providing details specific to products, sites, and suppliers, which allows third parties to assess product-specific risks on an ongoing basis. Shionogi reveals whether sites discharge beneath safe levels, discloses results clearly and supports ethical procurement.

GSK and Novartis are the only other companies to publicly disclose some information on compliance, though a lack of detail makes it hard to assess which of their sites and products might pose a risk for AMR. GSK discloses that all 20 of its own sites and 32 of 45 supplier sites comply with discharge limits. Novartis reports that 80% of its own sites comply with pharmaceutical limits, though the company's data is not specific to antibacterials.

NEXT STEPS

Shionogi says it will consider making publicly available the details of how it performs mass balance calculations to show the quantities of product discharged during production. It also commits to disclosing to the Benchmark actual details of audit results. To progress further, it could name other supplier locations on a city level to increase understanding of its supply chain and associated AMR risks.

Other companies should follow Shionogi's lead and take steps to disclose locations of suppliers, how many sites have safe levels of discharge, and compliance on a per-product basis. Since AMR-related risk also arises downstream, the Benchmark looks for companies to disclose details of external wastewater treatment plants, helping to ensure use of appropriate technologies and protocols can minimise the spread of resistance.

APPROPRIATE ACCESS: BEST PRACTICE 1

Pfizer and Viatris use registration to expand availability of on-patent antibiotics in low- and middle-income countries

PFIZER AND VIATRIS

Topic: Registration of on-patent antibiotics
What: Pfizer and Viatris have each expanded registration of specific on-patent medicines in more than 15 low- and middle-income countries since the last Benchmark.
Region: 102 low-and middle-income "access" countries

Antibacterial and antifungal medicines and vaccines are essential for treating and preventing infectious diseases. Yet millions of people live without reliable access to them or lack information to use them properly. When companies do not file to register new and on-patent medicines in countries in need, low availability can also increase the risk of resistance. Patients may purchase or be prescribed medicines that do not meet medical need or quality standards.

Registration is an important step to ensure products are made available for sale, especially in countries with higher levels of disease and inequality. Companies can show a commitment to enter markets in need by filing for registration with local regulatory authorities as widely and rapidly as possible after a product is first approved.

Which companies demonstrate best practice?

Pfizer and Viatris are the only companies to have expanded registration to on-patent antibiotics, submitting filings in additional low-and middle-income countries for specific products. Since the last Benchmark, Pfizer has filed its reserve antibiotic ceftazidime/avibactam (Zavicefta™) in 18 further countries including three low-income countries (Ethiopia, Tanzania, and Uganda). When implementing its access strategy for antimicrobials, Pfizer takes account of factors relating to patient and provider needs, and the ability for products to be used in consistency with its stewardship principles. The antibiotic, approved in 2016, plays a key role in treating complicated intra-abdominal infections and hospital-acquired pneumonia, which can both be fatal. Zavicefta™ is now registered in a total of 20 of the 102 low- and middle-income countries in the Benchmark assessment, including Brazil and India.

Viatris newly filed its anti-tuberculosis medicine pretomanid (Dovprela) for registration in 23 access countries including five low-income countries (Democratic Republic of Congo, Ethiopia, Mozambique, Tajikistan and Zimbabwe). Almost all countries where Viatris registered pretomanid since 2020 have tuberculosis burdens that the WHO judges to be among the world's highest. The medicine was developed by the TB Alliance and was first approved by the FDA in 2019. It is used for difficult-to-treat tuberculosis (XDR-TB and treatment-intolerant/non-responsive MDR-TB). Significantly, Viatris filed rapidly (within 12 months of receiving its first approval) in India, which has one of the highest burdens of tuberculosis.

NEXT STEPS

Especially in the case of key antibiotics, the Benchmark expects companies to improve access through registration. Filing can help companies increase patient reach and cut inappropriate use of antibiotics. Market size, financial opportunities and unclear local regulatory requirements may prevent companies from filing a product for registration in a specific country: in response, certain initiatives (such as the WHO Collaborative Registration Procedure and The African Medicines Regulatory Harmonization programme) can provide companies with support for product registration. Having local or regional offices in low- and middle-income countries may facilitate companies in submitting registration dossiers.

Pfizer, which demonstrates best practice, intends to expand access further in additional countries. It could consider filing for registration in countries with high burdens of intra-abdominal infections, complicated infections of the urinary tract or lower respiratory tract infections. Viatris could expand registration of pretomanid by filing for registration in more access countries, in particular the countries with a high burden of MDR-TB identified by the WHO, where it has commercialisation rights.

Few online regulatory databases yet track the registration of medicines in smaller, lower income countries. While regulatory agencies in low-and middle-income countries may lack the capacity for building and updating such databases, companies can play a role by increasing transparency about where they file products for registration. For example, Johnson & Johnson is the only company in scope to publicly disclose where it filed its MDR-TB medicine (bedaquiline). Companies should keep expanding registration to the most countries and make commitments for future action.

APPROPRIATE ACCESS: BEST PRACTICE 2

Viatris leads in strategies to expand access to TB treatment (pretomanid)

VIATRIS

Topic: Expanding access to on-patent antibacterial medicines
What: Viatris uses a variety of strategies to improve the affordability of its anti-TB medicines among underserved populations in countries in scope, and expand access.
Region: 102 low-and middle-income countries ("access countries")

According to WHO, tuberculosis (TB) deaths increased in 2020 for the first time in more than a decade, rising to 1.5 million. The situation is expected to worsen in 2021. Currently, 4,100 people die from TB daily. Between 2018 and 2020 across all adult age groups, only half of those with TB were treated, and just 41% percent of children.

More broadly, people need appropriate access to new and on-patent antibacterial medicines. Lack of availability and/or supply may lead patients to take medicines that do not meet medical need or quality standards, increasing the risk of AMR. In resource-limited countries with high burdens of diseases such as TB, challenges around appropriate access to products remain significantly higher. To expand access, companies can plan and implement a range of strategies to address product registration, accessibility, affordability and supply chains.

What does best practice look like?

Viatris has expanded access to its TB medicines. The company, formed in 2020 from the merger of Mylan and Upjohn, combines a variety of strategies to increase access. Pretomanid (Dovprela) is a relatively new medicine, developed by the TB Alliance and first approved by the FDA in 2019. It is part of the BPal (bedaquiline, pretomanid and linezolid) regimen to treat patients with extensively drug-resistant TB (XDR-TB) and treatment-intolerant/non-responsive MDR-TB. Viatris partners with the GDF-Stop TB Partnership to provide pretomanid at a defined global access price to 150 countries and territories, including all 102 low- and middle-income countries in scope of the Benchmark. A six-month course of treatment costs USD 364 (USD 2 per tablet). Viatris also distributes a generic version of delamanid (Deltyba™, produced by Viatris under licence from Otsuka) to treat MDR-TB.

Why does Viatris stand out?

Viatris stands out in its proactive approach to reach more people with its TB medicines in more countries, including those with the highest TB burdens. By using and combining a range of strategies, Viatris shows willingness and commitment to provide access to its TB medicines. The company's clear, well-described and detailed access strategies – stating patient and geographic reach, considering ability to pay, and indicating price level – meet the criteria for gold standard. The company also makes commitments for future access.

As well as its partnership with GDF-Stop TB, Viatris partners with other stakeholders including the KNCV in Ukraine, where the BPal regimen was introduced in 2020. Additionnal programmes are planned in Tajikistan, Myanmar, Vietnam, the Philippines and Indonesia. Another strategy is donations: the company provided 400 cumulative treatment courses of pretomanid, shared between the Indian National Tuberculosis Elimination Program and the South African Conditional Access Program. To ease local healthcare budget constraints, it also agreed to donate 50 courses each to Uzbekistan and Kyrgyzstan for research programmes.

A third initiative is a named patient access programme. Such programmes are not sustainable in the long-term but do take account of affordability to help ensure fast access to new medicines in low- and middle-income countries, acting as a shortcut to innovative and needed medicines. Viatris undertakes to offer pretomanid to up to 40 eligible patients per year in every country where it is not registered or available for free (or on par with GDF access pricing). Low- and lower-middle-income countries will be offered a price on par with GDF's and Viatris will expand the programme if demand increases.

Otsuka has a voluntary licensing agreement with Viatris to accelerate access to delamanid in high TB-burden countries. These two companies have entered into a technology transfer agreement allowing Viatris to produce a low-cost generic version of delamanid in India. The delamanid produced by Viatris does not currently meet quality assurance requirements as it is not approved by a Stringent Regulatory Authority or the WHO Prequalification Programme.

NEXT STEPS

Companies should consider the full range of access strategies from the toolkit to determine what is most appropriate, such as voluntary licensing, partnering with external stakeholders, patient assistance programmes, and equitable pricing policies. Companies should also take affordability into account, ensuring that their medicines and vaccines are affordable to the most people, including in the poorest countries.

APPROPRIATE ACCESS: BEST PRACTICE 3

Tech transfers and support for local manufacturing hubs to increase local availability of medicines and vaccines

AUROBINDO, GSK, NOVARTIS, OTSUKA, PFIZER, SANOFI, VIATRIS

Topic: The creation of local hubs to manufacture antibiotics
What: Seven companies are involved in technology transfers and other initiatives to enable antibacterial and antifungals medicines and vaccines to be produced locally.
Region: 8 countries (Brazil, China, India, Nigeria, Pakistan, South Africa, Vietnam, Zambia).

When supply chains are fragile or demand increases unexpectedly, this can lead to shortages in medicines and vaccines. Since these products can be produced through sensitive, multi-stage and highly technical processes, multiple manufacturers need to master these processes to ensure that supply can meet demand, and to minimise the impacts of shutdowns. Shorter supply chains can reduce the risk of fragmentation and stockouts and enable people to access a wider range of products.

Antibiotic production can be hampered by low profitability and low sales volumes. Companies that make these medicines should also aim to supply them continuously in low-and-middle income countries, where people lack access to affordable, quality-assured products. This involves creating transparency around supply chains for antibacterial and antifungal medicines and vaccines and working toward improving local manufacturing capabilities and working with multiple API suppliers.

What does best practice look like?

To support the development of local manufacturing in low- and middle-income countries, companies are investing in building capacity and sharing skills, knowledge, technologies, and manufacturing methods with local manufacturing partners. Initiatives need to be sustainable, enabling more countries and regions to produce their own medicines and vaccines locally over the long term. Ten companies report that they are supporting local manufacturing (such as by carrying out technology transfers) in at least one of the 102 low- and middle-income countries in scope.

Africa accounts for nearly 17% of the world's population, but produces only 3% of the medicines and 1% of the vaccines it consumes. Seven companies report technology transfers to African countries to produce antibiotics or antifungals medicines or vaccines locally.

Pfizer is working with the South African government and Biovac Consortium Cape Town to produce its pneumococcal vaccine (Prevnar13®) locally, taking raw materials through to the release of fully packaged products. It has developed automative processes to standardise the complex formulation of its vaccine, facilitate transfer of technology and reduce manufacturing risks.

Otsuka is working with Viatris (previously Mylan) to transfer technology to produce and distribute delamanid (Deltyba®). The first phase included initial manufacture, package and distribution of delamanid in access countries. From 2021, full API manufacturing will enable the generic version of delamanid to be made available in access countries including South Africa and India and to be procured through the Global Drug Facility following WHO-prequalification.

In Nigeria, Sanofi has worked since 2008 to produce medicines locally, including the antibiotic metronidazole (Flagyl®). It helps local plants meet quality standards and upgrade capabilities.

In Brazil, GSK partners with three state-owned vaccine manufacturers to produce priority vaccines, including antibacterial vaccines. It is transferring manufacturing practices such as formulation and packaging, technical know-how, and analytical testing methods. GSK aims to upgrade infrastructure, develop local capabilities, and train employees in good manufacturing practices. Through this, Brazil will be enabled to produce at least 60 million vaccine doses annually for its population.

Novartis partners with third parties in Pakistan to transfer manufacturing knowledge and produce products locally, including its Sandoz penicillin portfolio. As the development of effective new antibacterial medicines is failing to keep pace with resistance, older medicines such as penicillin have a role to play.

Aurobindo's manufacturing facilities are located in India. It supplies APIs to low- and middle-income countries and aims to improve their capacity to produce finished medicines.

NEXT STEPS

Companies need to develop local manufacturing sites and share knowledge, especially in resource-poor regions with high demand such as sub-Saharan Africa. The Benchmark looks for companies to build capacity and/or transfer technologies to cover more products and enable countries to become more self-sufficient and distribute their own medicines. Companies are expected to make commitments for future action and to include transfers of technology in their strategy and reporting.

Lack of capability and training are significant challenges. Companies that demonstrate best practice often partner with others and/or open offices locally. They also work with other stakeholders (such as governments and NGOs) to plan transfers of technology to enable products to be made sustainably.

STEWARDSHIP: BEST PRACTICE 1

Shionogi continues to fully decouple sales agents' bonuses from sales volumes of antibacterial medicines

SHIONOGI

Topic: Mitigating the risk of overselling
What: Shionogi is steadfast in fully decoupling its financial rewards for sales agents from the volume of antibacterial and antifungal medicines they sell, in order to mitigate the risk of overselling
Region: Global

One of the main drivers for the emergence of antimicrobial resistance (AMR) is the inappropriate use of antibacterial and antifungal medicines. When companies rely on making high volumes of sales, their resulting sales practices can lead to the promotion of overuse and misuse. Steps need to be taken to ensure products are used only when needed.

By avoiding the use of sales agents altogether for antibacterials and antifungals, companies can reduce their risk of overselling to healthcare professionals and the prescription of unneeded medicines. Companies that do retain a sales force can decouple incentives for their agents from sales volumes, so that bonuses do not depend on how much product is sold.

Why does Shionogi lead?

Shionogi was the first large research-based pharmaceutical company to fully decouple its incentives for sales agents from sales volumes. It began in Japan in 2016 and extended the practice globally the following year. The Benchmark recognised this as best practice in 2020.

The company does not link the payment of bonuses to the volumes its sales agents sell. It incentivises agents instead through linking to competencies such as interactions with healthcare professionals and knowledge of AMR. No other company in scope has fully decoupled such incentives for its agents globally. Just as importantly, Shionogi applies this practice globally for all products in scope, and is consistent in maintaining the practice.

Cipla, the first generic medicine manufacturer to fully decouple its incentives for agents globally, was recognised for best practice in 2020. It now links <1% of its incentives to sales volumes. GSK pioneered the practice in 2013 but now no longer fully decouples. Other companies decouple incentives only for some products and/or in selected regions. Only Shionogi applies the practice across the board.

NEXT STEPS

To improve further, Shionogi could choose to cease altogether the promotion of its products to healthcare professionals. Companies such as Abbott, Pfizer and MSD, which have run decoupling pilot projects, can expand this practice to more countries and products. Incentives for sales agents can be awarded at individual, smaller group or national level. When incentives are awarded at national and smaller group (rather than individual) level, they are linked less directly to total pay, so that when an individual agent sells a higher volume of products, this does not directly increase that person's total pay. All companies can follow Shionogi's lead and fully decouple incentives on a global basis, and maintain this practice to minimise the spread of resistance.

STEWARDSHIP: BEST PRACTICE 2

No sales teams for anti-tuberculosis medicines, to shrink the risk of overselling

VIATRIS, OTSUKA, JOHNSON & JOHNSON

Topic: Mitigating the risk of overselling

What: Viatris, Otsuka and Johnson & Johnson have stopped their use of sales agents to promote their tuberculosis medicines to healthcare professionals in order to minimise the spread of resistance

Region: Global

When antimicrobial products are used too much or wrongly, they can become ineffective and drive AMR. Companies that rely on making high volumes of sales may deploy sales practices that lead to overselling and promote inappropriate use. When companies choose not to promote their products, they can mitigate this risk and help to limit resistance.

Given the wide spread of multidrug-resistant and extensively drug-resistant tuberculosis (MDR-TB and XDR-TB), it is crucial that new medicines do not become ineffective. These are medicines of last resort, and global health and national public health bodies recommend they be made available only in specialised centres under tightly controlled conditions.

What does best practice look like?

Otsuka, Johnson & Johnson and Viatris have chosen not to promote their on-patent tuberculosis medicines (respectively delamanid/Deltyba®, bedaquiline/Sirturo® and pretomanid/Doprevla) in most countries, despite having received marketing authorisation. Johnson & Johnson does promote bedaquiline (Sirturo®) in at least one country. These are the only three on-patent medicines for the disease: the first two are used to treat MDR-TB, while the newer Dovprela (first approved in 2019) treats XDR-TB, non-responsive MDR-TB and treatment-intolerant TB.

By choosing not to promote, these three companies remove the risk of incentivising sales agents to oversell to healthcare professionals. In 2020, the Benchmark recognised Otsuka and Johnson & Johnson for best practice: both remain consistent in their approach.

NEXT STEPS

It is especially important that strong stewardship measures are used for new medicines to help patients who do not respond to other treatment. Promotion can lead to overselling and weaken treatment effectiveness. The decision to not promote these medicines is a significant step in the right direction.

Many companies still promote their antibacterial and antifungal medicines to healthcare professionals. In the case of last-resort antibiotics (such as those the WHO classifies as "reserve"), the Benchmark urges manufacturers to avoid promotion to mitigate overselling, misuse and the spread of resistance.

STEWARDSHIP: BEST PRACTICE 3

GSK adapts Augmentin™ packaging to suit a range of patient needs and support its responsible use

GSK

Topic: Improving the appropriate use of antibacterial medicine by adapting packaging and brochures
What: GSK has adapted the way it presents amoxicillin/clavulanic acid (Augmentin™) to help patients use the product in appropriate ways
Region: 44 countries

One of the main drivers for the emergence of resistance is the misuse of antibacterial and antifungal medicines. When patients do not complete a full course of treatment, for example, this can contribute to the conditions that make medicines ineffective.

Medicines prescribed or bought over the counter are more likely to be used appropriately if they come with high-quality information. Companies can adapt their brochures and packaging to help patients with this. Brochures might be written in local dialects, or pictograms may be used if illiteracy is an issue for the population.

How does GSK demonstrate best practice?

Two-thirds of the companies in scope (11 of 17) make at least one adaptation. Very few make changes to consider multiple patient needs: Abbott and Pfizer have three, and three companies report two. GSK is the only company to take full account of the range of differing patient needs.

GSK takes account of a range of identified needs to ensure it helps patients to use amoxicillin/clavulanic acid (Augmentin™) appropriately. GSK has considered language, ability to adhere to a regimen, environmental conditions, levels of literacy and paediatric use. No other company in scope has adapted its brochures and/or packaging in accordance with this range of needs.

Augmentin™ is a widely used antibiotic, a type of penicillin that treats bacterial infections. For Mauritius, Angola and Mozambique, GSK has translated its patient knowledge card into French and Portuguese: this card also highlights information to help patients continue the course of the medicine as prescribed. For patients in Pakistan, a high-humidity environment, GSK has created a bespoke blister packaging with a lidding foil sensitive to moisture. In Gulf Cooperation Council regions with low levels of literacy, GSK deploys an AI-enabled chatbot that uses graphics in a smartphone application to educate patients. The company also offers oral suspensions and flavoured dosing syringes across 35 countries to help children take the medicine.

NEXT STEPS

No standards yet exist for the development and use of adaptations, but GSK demonstrates that it is possible to combine a range for optimal effectiveness. The Benchmark expects companies to be proactive and creative, and take steps to help patients use their medicines well. It looks for common-sense adaptations for all products where appropriate, and for commitment to future action.

STEWARDSHIP: BEST PRACTICE 4

Pfizer remains only company to share raw data on AMR surveillance, adding countries and pathogens

PFIZER

Topic: AMR surveillance
What: Pfizer has expanded its AMR surveillance programme to include more priority pathogens and more countries, and continues to share its raw data publicly to increase stakeholder insight
Region: 81 countries (global)

Data on AMR surveillance helps governments, public health authorities and healthcare professionals measure and respond to infections, analyse local trends and prioritise objectives in stewardship policies. Companies involved in surveillance to monitor resistance of pathogens against antibacterial and/or antifungal medicines need to share their raw data publicly, so experts, researchers and healthcare professionals can use it. Access can help stakeholders to forecast disease trends; plan medicine purchases; make better-informed treatment choices; and improve policy directives and investment decisions for laboratory capacity, infection prevention and control response, and identification of newly emerging pathogens.

Through its Antimicrobial Testing Leadership and Surveillance (ATLAS) programme, which began in 2004, Pfizer works with UK-based curator Micron Research to monitor pathogen resistance against the antibacterial products it markets and is developing. ATLAS monitors changes in antibiotic susceptibility, bacterial resistance trends and emergence of new resistance strains. Around 48,000 bacterial isolates are collected each year and Pfizer updates the database every six months.

How does Pfizer lead?

Pfizer was the first company in scope to share raw data from ATLAS (from 2018) on the AMR Register, an open-access data platform set up by Open Data Institute and Wellcome Trust. In 2020, the Benchmark recognised this as best practice. Data can be downloaded from the site, while aggregated data is made available via the ATLAS website to anyone who registers with an email address.

Since 2020, through the ATLAS website, Pfizer has chosen to share new aggregated data on antifungal resistance. It has also expanded its programme to include new priority pathogens and countries, with a focus on Africa. Of all AMR surveillance programmes operated by companies in scope, Pfizer's covers the most priority pathogens (13), up from nine in 2020. A collaboration with the governments of Ghana, Malawi, Kenya and Uganda (Surveillance Partnership to Improve Data for Action on Antimicrobial Resistance, or SPIDAAR) has seen it expand its programme to 81 countries (from 73 in 2020).

NEXT STEPS

The Benchmark looks for all companies involved in AMR surveillance to make a commitment to share their raw data in an easily accessible way, such as through the AMR Register. Pfizer, which already leads, could continue to expand its programme to cover surveillance of resistance in further countries.

No company except Pfizer yet reaches the gold standard. Other companies share aggregated results through open-access data platforms and/or in open-access journals. Johnson & Johnson shares raw data from clinical trials through a mechanism that involves requesting access, which is more restrictive. GSK and Shionogi both report they intend to publicly share raw data but have not done so yet, while MSD intends to also share data through a mechanism that involves requesting access.

Sharing raw data enables public health bodies and professionals to use it in a range of valuable ways. Raw data can be used for studies on the burden of AMR, including the IHME Global Burden of Disease study on AMR morbidity or mortality (the GRAM project). It can provide valuable insights into where resistance to medicines occurs, and may help predict which medicines will be ineffective because of resistance, facilitating better treatment choices.

Company Report Cards

The 2021 Antimicrobial Resistance Benchmark includes a set of 17 company report cards, providing a detailed overview of each company's performance. Companies are all different in the way they operate, where they operate, and in their portfolio of investigational and marketed products.

The Report Cards are divided into six sections:

Performance
Explains the company's performance in the 2021 Benchmark, including the drivers behind any movement, and the main areas where it scores well or poorly compared to its peers.

Opportunities
Sets out tailored opportunities for the company to do more to ensure access and address AMR, taking account of its R&D pipeline (where applicable), product portfolio, and othrer factors.

Changes since 2020
Highlights the most notable changes in the company's performance since the 2020 Benchmark, including a selection of new or expanded activities and programmes.

Sales and operations
Summarises the company's global operations, revenue per product and region, including mergers and acquisitions relevant to antibacterial and antifungal products.

Pipeline and portfolio
General description of the company's operations, recent mergers & acquisitions, revenue per region, and geographical reach.

Performance by Research Area
Details the company's performance in each of the three areas measured by the Benchmark: R&D, Responsible Manufacturing, and Appropriate Access and Stewardship.

Overall Performance

2020 2021

86% **84%▼**

GlaxoSmithKline plc

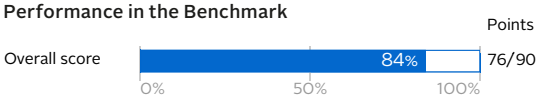
Large R&D-based pharmaceutical company

Stock exchange: LSE • Ticker: GSK • HQ: Brentford, UK • Employees: 94,066

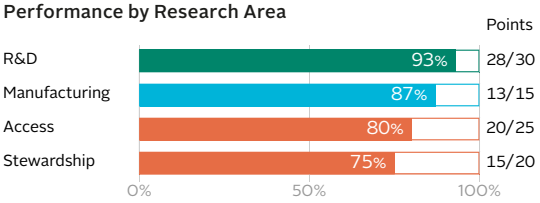
PERFORMANCE

GSK is the leader among the large research-based pharmaceutical companies in scope and performs well in its evaluated Research Areas.
R&D: With 31 R&D projects, about half of them vaccines, GSK leads in R&D. Eleven of its projects target critical and/or urgent pathogens. Two of its medicine candidates in clinical development are novel. GSK reports access and/or stewardship planning for all five of its late-stage projects.
Responsible Manufacturing: Performs strongly. Reports comprehensive environmental risk-management strategy for own sites and suppliers; co-leads in reporting compliance with limits at own sites and suppliers; publicly discloses this compliance.
Appropriate Access: Performs strongly. Files some of its on- and off-patent products for registration in access countries. Reports several strategies to expand access and ensure continuous supply to its on-patent antibacterial vaccines in access countries.
Stewardship: Performs well. It partly decouples incentives for sales agents from sales volumes. It publicly shares aggregated results of its SOAR surveillance programme. It reports broad conflict of interest mitigation for its educational programmes. It adapts brochures and packaging for patients.

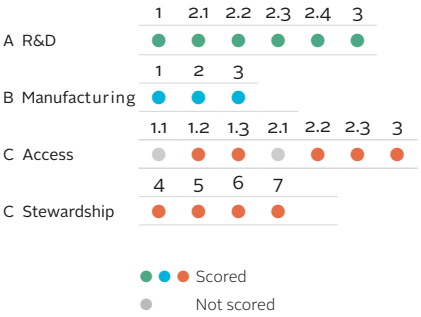
Performance in the Benchmark



Performance by Research Area



How GSK was evaluated



OPPORTUNITIES FOR GSK

Expand and tailor access and stewardship plans for critical late-stage R&D projects. As a leader in antibacterial and antifungal R&D with the largest pipeline, GSK can further strengthen their company-wide policies and project-specific plans to ensure new medicines are swiftly available to those in critical need but also to prevent excessive use. GSK maintains policies and plans for their late-stage R&D projects and can make plans more wide-reaching and timely. As an example, for its vaccine Bexsero®, that is in phase III targeting *N. gonorrhaeae*, GSK can define the access countries where it plans to file for registration, based on burden of disease and where resistance for *N. gonorrhaeae* is highest and where it considers ability-to-pay in its pricing strategy. In addition, GSK can expand its stewardship plans for its medicine R&D projects through more comprehensive surveillance activities by covering more priority pathogens and countries, as well as re-evaluating its sales practices for when these medicines reach the market to safeguard them from overuse and misuse.
Increase public disclosure on environmental risk management. GSK publishes information on some of the components of its environmental risk-management strategy including compliance percentages of its own and suppliers' sites with discharge limits. While it reports 100% compliance at its own sites, it can disclose more information to provide clear evidence of its progress publicly. Disclosure of information, including the results of audits and antibacterial discharge levels of its own sites and suppliers' sites, is important. It can also publicly disclose the names and locations of its suppliers and waste-treatment plants for increased transparency. GSK can also apply limits directly in effluent to fully mitigate AMR risk.
Comprehensively mitigate COI for educational programmes. GSK organises medical education programmes for healthcare professionals on responsible use of antimicrobial medicines. It ensures that branded materials are not used in most educational programmes. It can ensure that this is applied in all educational programmes.
Fully decouple incentives for sales agents from sales volumes. GSK links part of its sales agents' incentives to sales volumes of antibacterial and antifungal medicines. It can fully decouple incentives for sales agents from sales volumes again.
Publicly share raw data from surveillance programme. GSK runs the multinational Survey of Antibiotic Resistance (SOAR) programme, which is focused on community-acquired respiratory-tract infections. It can publicly share raw data from this surveillance programme, following through on clear commitments to share this with the University of Washington (as part of the GRAM project) and on the AMR Register.

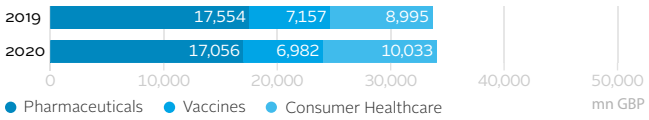
CHANGES SINCE 2020

- In February 2020, GSK joined the Project to Accelerate New Treatments for Tuberculosis (PAN-TB), a collaboration among philanthropic, non-profit and sector partners that aims to develop an investigational drug regimen capable of treating all forms of TB.
- Compared to 2020 Benchmark analysis, GSK tracks the compliance of its own and suppliers' sites with discharge limits. All of GSK's own sites and 95% of its suppliers' sites are reportedly compliant with discharge limits.
- Since 2020, GSK has publicly shared information on compliance percentages of own and suppliers' sites, specific to antibacterial production.
- GSK received funding from CARB-X, up to USD 18 mn, to support the development of two unique vaccine projects that target the prevention of group A streptococcus (Strep A) infections and infections caused by *Salmonella enterica* which cause invasive nontyphoidal salmonellosis (iNTS) disease and typhoid fever. Currently there are no vaccines available against these infections.

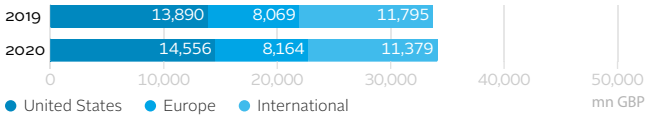
SALES AND OPERATIONS

Therapeutic areas: Respiratory, HIV, Immuno-inflammation, Oncology
Business segments: Pharmaceuticals, Consumer healthcare, Vaccines
Product categories: Innovative medicines, Vaccines, Consumer health products
M&A since 2020: In July 2019, GSK and Pfizer combined their consumer health care business in a new joint venture, with GSK having the majority and controlling an equity interest of 68%. In February 2021, GSK signed an agreement to sell the cephalosporin antibiotic business to Sandoz (Novartis division) for USD 350 mn in addition to milestone payments up to USD 150 mn.

Turnover by business segment



Turnover by region



PIPELINE *for pathogens in scope*

Pipeline size: 31 projects targeting pathogens in scope* (15 antibacterial medicines; 15 antibacterial vaccines; 1 antifungal vaccine)
Development stages: 10 clinical projects, 5 in Phase I, 2 in Phase II and 3 in Phase III, including a Phase III project for an expanded indication of its serogroup B meningococcal vaccine (Bexsero®) for the prevention of gonorrhoea; and 19 discovery/preclinical projects.
Novelty: 2 novel projects, GSK-3036656, for the treatment of *Myobacterium tuberculosis*, that meets all four WHO innovativeness criteria; and gepotidacin, for the treatment of infections caused by *Enterobacteriaceae* and *Neisseria gonorrhoeae*, and which belongs to a new chemical class and has a new mode of action.
'Critical' and/or 'urgent' pathogens: 11 projects, with the focus on carbapenem-resistant *Escherichia coli* and drug-resistant *N. gonorrhoeae*. GSK has one vaccine against *C. difficile* in Phase I of clinical development.
Regulatory approvals: 0 approvals for products targeting pathogens in scope.

PORTFOLIO *for pathogens in scope*

Mid-sized portfolio: At least 51 products: 28 antibacterial medicines; 19 antibacterial vaccines; 4 antifungal medicines
On-patent vaccines: 8 (Infanrix® IPV Hib, Infanrix® Hexa, Boostrix®, Infanrix® Hib, Boostrix® Polio, Menveo®, Bexsero®, Synflorix®)
Off-patent/generic medicines: 9 of 43 were selected for analysis* (amoxicillin [A], amoxicillin/clavulanic acid [A], cefadroxil [W], cefuroxime [W], clotrimazole [F], colistin [R], dapsone [T], griseofulvin [F], polymixin B [R])
AWaRe medicines:** 8 Access group; 9 Watch group; 2 Reserve group
Anti-TB medicines:** 1

Pipeline for priority pathogens

Products on the market

PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT Evaluated: medicine & vaccine pipelines for priority* bacteria & fungi

A.1 Largest amount invested in R&D
GSK reports to the Benchmark the amount invested during 2019 and 2020 in R&D for antibacterial and antifungal medicines and/or vaccines for pathogens in scope. Specific investment figures were provided under confidentiality. GSK reports above average R&D investments relative to its revenues among the companies assessed. GSK reports the largest absolute R&D investment figure compared to the other companies who reported investments to the Benchmark. GSK is a contributor to the AMR Action Fund.

A.2.1 GSK has the largest R&D pipeline among the large R&D-based companies
The company reports 31 projects targeting pathogens in scope: 15 medicines and 16 vaccines, targeting bacterial and fungal pathogens. Out of the 31 projects, ten are in clinical development, 19 are in discovery/preclinical stage and 2 projects are in technical lifecycle. GSK did not obtain marketing approval for any of its products during the period of analysis.

Pipeline targeting priority pathogens: 31* *As at 24 September 2021*

Discovery	Pre-clinical	Phase I	Phase II	Phase III	Approval
IMI ENABLE or Shigella	♦ Enteric fever (bi-valent conjugate) vaccine [*S. enterica* (typhi & paratyphi A)] ♦ Invasive non-typhoidal *Salmonella* (iNTS; bi-valent GMMA) vaccine [*S. enterica* serovars typhimurium + enteritidis] ♦ *Shigella spp.* (multivalent GMMA-based) vaccine ♦ Invasive non-typhoidal *Salmonella* (iNTS; bi-valent GMMA) vaccine [*S. enterica* serovar Typhimurium + Enteritidis & conjugate for *S. enterica* serovar Typhi)] ♦ Group A Streptococcus (4-valent recombinant conjugated adjuvanted) vaccine	♦ *C. difficile* vaccine (GSK2904545A) ♦ *Staphylococcus aureus* vaccine (GSK3878858A) FimH (GSK3882347) [*E. coli*]	GSK-070 (GSK-3036656) [*M. tuberculosis*] ♦ *M. tuberculosis* prophylactic vaccine [GSK692342/SB692342; M72/AS01E]	Gepotidacin [*E. coli*] Gepotidacin - additional indication [*N. gonorrhoeae*] ♦ *N. gonorrhoeae* vaccine (Bexsero®) - additional indication of serogroup B meningococcal vaccine	

♦ Vaccine
GMMA = Generalized modules for membrane antigens

* See Appendix V for information about eligibility for R&D projects and Appendix VII for eligibility criteria of products.
** Listed on the 2019 WHO EML.

*** Includes 17 projects not shown in the figure: 15 projects provided to the Benchmark on the basis of confidentiality and 2 projects in technical lifecycle (heat-stable and cold-stable formulations of GSK's *Streptococcus pneumoniae* (Synflorix®) vaccine).

A.2.2 Pipeline with highest number of innovative candidates

GSK's clinical-stage medicine pipeline consists of both innovative and adaptive R&D projects. GSK has four innovative medicine antibacterial candidates in clinical development, making the company's clinical pipeline the one with the highest number of innovative candidates among all companies evaluated in the Benchmark. This includes GSK-3036656, for the treatment of tuberculosis, which meets all four WHO's innovativeness criteria; and gepotidacin, for the treatment of infections caused by *Enterobacteriaceae* and *N. gonorrhoeae*, which belongs to a new chemical class and has a new mode of action. GSK also has a non-traditional medicine in clinical development.

A.2.3 Largest vaccine pipeline

GSK reports 16 vaccine projects in its pipeline. It is by far the largest vaccine pipeline of the six companies active in vaccine development. It includes 13 innovative and three adaptive projects. GSK's vaccines in clinical stages of development include candidates targeting *C. difficile*, *S. aureus* and *N. gonorrhoeae*. Moreover, GSK is developing M72/AS01E in collaboration with the Bill & Melinda Gates Medical Research Institute, a Phase II tuberculosis vaccine candidate.

A.2.4 Largest number of projects targeting 'critical' and/or 'urgent' pathogens

GSK has 11 projects targeting pathogens defined as 'critical' by WHO's list of priority pathogens and/or characterised as 'urgent' threats by the US Centers for Disease Control and Prevention (CDC). In clinical development, GSK has medicine candidates against Carbapenem-resistant/ESBL-resistant *E. coli* and *N. gonorrhoeae*; and vaccine candidates against *C. difficile* and *N. gonorrhoeae*.

A.3 Company-wide commitments and project-specific plans for access and stewardship

GSK has five late-stage R&D projects targeting pathogens in scope. It reports having project-specific access plans for most of these projects. All five projects have ongoing trials in access countries.†

GSK reports that it has developed an equitable pricing strategy framework for low- and middle-income countries (LMICs) that applies across its portfolio and business units. Its access plans include equitable pricing strategies, registration filings, non-exclusive licensing and supply chain commitments. GSK states that it does not file patents in Least Developed or Low-Income countries nor does it enforce historic patents. GSK does not conduct clinical trials in countries where it does not intend to pursue registration and to make the product available for use. GSK commits to conducting global surveillance studies for its new antibacterials to enable appropriate use and support stewardship.

B RESPONSIBLE MANUFACTURING Evaluated: antibacterials manufacturing (APIs and drug products)

B.1 Comprehensive environmental risk-management for own sites and suppliers; tracks compliance with limits at own sites and suppliers

GSK reports a comprehensive strategy to minimise the environmental impact of wastewaters and solid waste from antibacterial manufacturing at its sites, including audits every three years. It reports setting discharge limits in the receiving environment for all antibacterials manufactured at its sites, based on PNECs to limit AMR, as recommended by the AMR Industry Alliance. Discharge levels are quantified at all sites using a mass balance approach, verified by chemical analysis if applicable. GSK reports that all its 20 sites, or 100%, are compliant with discharge limits.

GSK requires third-party suppliers of antibacterials to follow the same standards, including limits based on PNECs. It reports conducting on-site audits every three years. It requests and reviews the discharge levels of its suppliers. It reports 37 of 39 supplier sites, or 95%, are compliant with discharge limits.

GSK expects external private waste-treatment plants to comply with its general environmental standards. GSK audits these plants at least every 3 years (based on risk) which includes checking the suitability of technologies used for processing waste and protocols for preventing contamination. It requests external private and public wastewater treatment plants for dilution and flow rate data to inform the mass balance approach and employs conservative measures when needed.

B.2 Publicly discloses some information on environmental risk management and compliance with limits

GSK publishes some components of its environmental risk-management strategy and is a member of the AMR Industry Alliance. It discloses that all its 20 (100%) own sites manufacturing antimicrobials and 32 of 45 (71%) of supplier sites are compliant with discharge targets set by the AMR Industry Alliance.‡ The discharge levels themselves are not published. It also does not publish: (1) the results of environmental audits, conducted at its own sites, the sites of suppliers and/or external private and public waste-treatment plants; or (2) a list of these suppliers and plants.

B.3 System in place to maintain production quality for own and suppliers' sites; no requests for official corrective action

GSK reports that its own sites and suppliers have a system to maintain high-quality antibacterial production consistent with international GMP standards. This includes periodic risk-based audits and tracking of corrective and preventive actions. GSK does not require its suppliers to audit their own suppliers, but do encourage them to do so. The Benchmark found no requests for official corrective action from the FDA or EMA related to non-conformities with cGMP at GSK's own sites or any subsidiaries that manufacture antibacterials.

C APPROPRIATE ACCESS & STEWARDSHIP – ACCESS

Evaluated: access activities relating to antibacterial & antifungal medicines & vaccines in 102 access countries†

GSK is not eligible for indicators: C.1.1 and C.2.1. For more information, see Appendix VII.

C.1.2 Filed to register off-patent/generic medicines in 16 access countries on average

GSK performs above average, filing eight of its nine relevant off-patent/generic medicines for registration in 16 access countries on average. Its most widely filed relevant product is the antibiotic amoxicillin/clavulanic acid filed in 62 access countries including 19 LICs. Seven of its relevant products are filed in less than 10 access countries.

C.1.3 Filed to register on-patent vaccines in 17 access countries on average

GSK has an average performance, filing seven of its eight relevant on-patent vaccines for registration in access countries. Its most widely filed relevant vaccine is the pneumococcal conjugate vaccine Synflorix®, filed in 45 access countries followed by Infanrix® Hexa, its vaccine used to protect against diphtheria, tetanus, pertussis, hepatitis B, polio and bacterial meningitis (Hib), filed in 31 access countries. Two of its eight relevant vaccines are filed for registration in at least one LIC.

† 102 low- and middle-income countries where better access to medicine is most needed.

‡ Discrepancy with compliance data in B.1 is explained by GSK's submission data for the Benchmark being more up to date than publicly available data.

C.2.2 Several strategies to expand access to off-patent/generic medicines

GSK performs above average. It aims to expand access to its off-patent/generic medicines in access countries through donations, second-brands, patient support programmes, tenders, and equitable pricing policies. GSK provides evidence of patient reach and geographic reach for all its reported approaches. For example, GSK donated more than 200,000 units of its branded amoxicillin/clavulanic acid antibiotic in 2020 through humanitarian partnerships, including one with Save the Children.

C.2.3 Several strategies to expand access to on-patent vaccines

GSK performs above average, with access strategies reported for all its eight relevant on-patent vaccines in scope. It aims to expand access to its on-patent vaccines in access countries through tiered pricing policies and public or private partnerships. GSK partners with MSF and UNICEF to provide Synflorix® at the lowest price tier during humanitarian situations. GSK provides evidence of patient reach and geographic reach for some of its reported approaches. For example, it estimates that 56 mn doses of Synflorix® were supplied to Gavi-eligible countries in 2020, through its partnership with Gavi The Vaccine Alliance.

C.3 Leader in strategies to ensure continuous supply

GSK performs above average, with strategies reported in all four areas assessed. GSK ensures accurate demand planning and data sharing by conducting 3-year forecasts and annual long-term demand forecasting (up to 10 years). GSK mitigates against shortage risks by keeping buffer stocks for both APIs and finished products. It ensures dual sourcing for critical APIs. GSK reports three capacity building or technology transfer initiatives in access countries, such as its support to the Strategic Training Executives Programme (STEP) in GAVI-eligible countries. To mitigate against substandard and falsified products, GSK works closely with local law enforcement, conducts online and offline investigations or uses security features such as serialised barcodes and tamper-evident packaging.

C APPROPRIATE ACCESS & STEWARDSHIP – STEWARDSHIP

Evaluated: stewardship activities relating to antibacterial & antifungal medicines globally

C.4 Broad COI mitigation strategies in place for its educational programmes

GSK performs well in conflict of interest (COI) mitigation for the five AMR-related educational programmes for HCPs assessed by the Benchmark. Four programmes have all three COI mitigation strategies looked for by the Benchmark: (1) content is developed independently from its marketing department; (2) a pledge not to provide financial or material incentives to participants; and (3) it does not use branded materials. The remaining programme has two COI mitigation strategies: in some countries where these programmes were presented the content could be branded.

C.5 Engages in sales and marketing practices to address appropriate use

GSK is middle-performing in sales practices. It reports that it partly decouples incentives for sales agents from sales volumes of its antibacterial and/or antifungal medicines. Its percentage of variable pay linked to sales volumes is 25%, and this is set at the smaller group level.

GSK engages in marketing practices that aim to address the appropriate use of its antibacterial and/or antifungal medicines. Its marketing materials reflect emerging resistance trends and/or include treatment guidelines for healthcare professionals. In some countries these include GSK SOAR surveillance data for the antibacterials amoxicillin/clavulanic acid (Augmentin™) and cefuroxime (Zinnat®).

C.6 Makes five types of brochure and/or packaging adaptations to facilitate appropriate use by patients

GSK adapts brochures and packaging to facilitate the appropriate use of amoxicillin/clavulanic acid (Augmentin™) by patients. GSK is the leader in this measure, taking account of language, adherence to treatment, literacy, the environment and paediatric use. For example, it has translated a Patient Knowledge Card into English, French and Portuguese. This card highlights information to improve adherence to treatment. Moreover, GSK has created blister packaging with a specific lidding foil that is sensitive to moisture for high humidity environments. Further, it has created oral suspensions and flavoured dosing syringes for paediatric patients in 35 countries.

C.7 Active in one AMR surveillance programme; openly publishes aggregated results

GSK runs the multinational Survey of Antibiotic Resistance (SOAR) programme, which is focused on community-acquired respiratory-tract infections in more than 30 countries and has been running since 2002. GSK only shares the aggregated results through peer-reviewed open-access journal articles. In addition, it will be sharing SOAR data with the University of Oxford and University of Washington (as part of the GRAM project) as well as on the AMR Register, an open-access data platform, with these projects aiming to complete in Q4 of 2021.

Overall Performance

2020 2021

68% **68%=**

Johnson & Johnson

Large R&D-based pharmaceutical company

Stock exchange: NYSE • Ticker: JNJ • HQ: New Brunswick, NJ, USA • Employees: 136,400

PERFORMANCE

Johnson & Johnson performs above average overall in its evaluated Research Areas compared to the other large research-based pharmaceutical companies in scope.

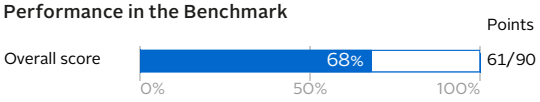
R&D: Johnson & Johnson is a middle-performing company in the R&D Research Area. Its 14-project pipeline has two vaccines. It has projects that target critical and/or urgent pathogens. Its two late-stage development projects are covered by project-specific access plans.

Responsible Manufacturing: Performs strongly. Reports comprehensive environmental risk-management strategy for own sites and suppliers; quantifies discharge levels at all own sites.

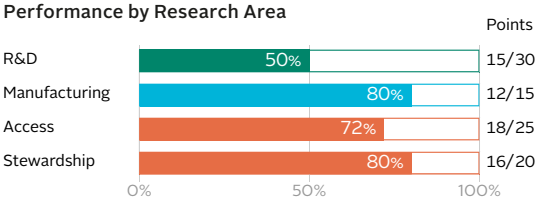
Appropriate Access: Performs well. Files some of its on- and off-patent medicines for registration in access countries. Reports some strategies to expand access and ensure continuous supply of its relevant products.

Stewardship: Performs well. It generally does not promote bedaquiline (Sirturo®) to healthcare professionals. It shares raw data of its DREAM surveillance programme in a restricted manner. It reports comprehensive conflict of interest mitigation for its educational programmes. It adapts brochures and packaging for patients.

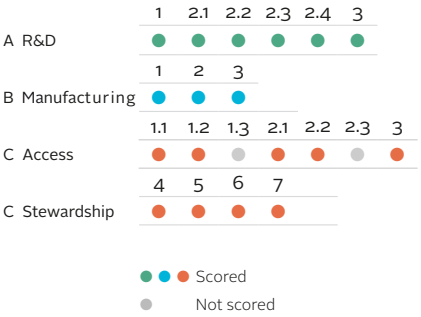
Performance in the Benchmark



Performance by Research Area



How Johnson & Johnson was evaluated



OPPORTUNITIES FOR JOHNSON & JOHNSON

Diversify access plans for late-stage R&D projects. Johnson & Johnson has one medicine and one vaccine in late-stage development. It can improve access to these new products, by developing plans for registration, affordability and sustainable supply. For example, for their phase III vaccine, ExPEC9V, Johnson & Johnson can define the access countries where they will file for registration, based on burden of disease, and where it considers ability-to-pay in its pricing strategy. Johnson & Johnson can also engage with external partners with the expertise to help boost availability of the vaccine in relevant territories once approved.

Ensure compliance with antibacterial discharge limits at own sites and suppliers by tracking and publicly disclosing progress and results. Johnson & Johnson reports to set limits and to quantify the discharge levels at its own sites and suppliers' sites. To provide clear evidence of its progress, it can track compliance at all sites and publicly disclose the results. Disclosure of information, including the results of audits and antibacterial discharge levels of its own sites and suppliers' sites, is important. It can also publicly disclose the names and locations of its suppliers and waste-treatment plants for increased transparency.

Expand reach of bedaquiline (Sirturo®) for eligible MDR-TB patients. Johnson & Johnson has continued to reach more patients with MDR-TB through tenders, patient assistance programmes, access price settings and public or private partnerships. It can further apply these mechanisms to expand access and ensure diagnosed patients are treated, especially in countries where gaps remain between diagnosis of MDR-TB and treatment.

Fully decouple incentives for sales agents from sales volumes. Johnson & Johnson does not promote bedaquiline (Sirturo®) in most countries. Johnson & Johnson can apply the practice of not promoting this product globally. Further, it can fully decouple incentives for sales agents from sales volumes of all antibacterial and antifungal medicines.

Publicly share raw data from surveillance programme. Johnson & Johnson runs the multinational Drug Resistance Emergence Assessment in MDR-TB (DREAM) programme, which is focused on resistance against bedaquiline (Sirturo®). It can publicly share raw data from this surveillance programme, anonymised and in a freely accessible format.

CHANGES SINCE 2020

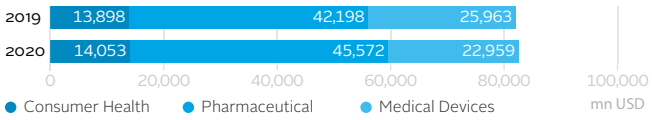
- Johnson & Johnson launched its inaugural satellite center for Global Health Discovery hosted at LSHTM focused on addressing the threat of AMR and TB.
- In February 2020, Johnson & Johnson joined the Project to Accelerate New Treatments for Tuberculosis (PAN-TB), a collaboration among philanthropic, non-profit and private sectors partners that aims to develop an investigational drug regimen capable of treating all forms of TB.
- Johnson & Johnson is funder and member of the consortium VALUE-Dx. VALUE-Dx is the first Innovative Medicines Initiative project initiated by six *in vitro* diagnostic companies who work with 20 non-industry partners to combat AMR and improve patient outcomes.
- Johnson & Johnson received two FDA indication extension approvals for bedaquiline (Sirturo®)* for MDR-TB in adolescents (12 - <18years) and pediatrics indications (5 - <12years).
- In 2020, Johnson & Johnson collaborated with the GDF Stop TB to reduce the price of bedaquiline in eligible low- and middle-income countries.

* As part of combination therapy of pulmonary tuberculosis due to multi-drug resistant *M. tuberculosis*.

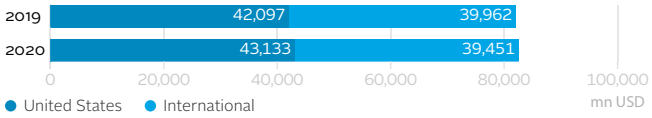
SALES AND OPERATIONS

Therapeutic areas: Cardiovascular/metabolism/(other), Immunology, Infectious diseases, Neuroscience, Oncology, Pulmonary hypertension.
Business segments: Consumer health, Medical devices, Pharmaceutical
Product categories: Consumer health products, Medical devices, Innovative medicines, Vaccines
M&A since 2020: None in the antibacterial and/or antifungal sectors

Sales by business segment



Sales by region



PIPELINE *for pathogens in scope*

Pipeline size: 14 projects targeting pathogens in scope** (12 antibacterial medicines; 2 antibacterial vaccines).
Development stages: 1 clinical project, ExPEC9V (formerly ExPEC10V) a Phase III, 9-valent vaccine for the prevention of invasive extraintestinal pathogenic *E. coli* disease in adults; and 12 discovery/preclinical projects.
Novelty: 0 novel clinical-stage medicine projects.
'Critical' and/or 'urgent' pathogens: Projects targeting invasive extraintestinal pathogenic *E. coli* (ExPEC) and *P. aeruginosa*.
Regulatory approvals: 2 approvals. In August 2019, marketing authorisation by the FDA was granted for the adolescent indication (12 - <18 years) of the MDR-TB drug bedaquiline (Sirturo®)* and in May 2020, for the paediatric indication (ages 5 - < 12 years).

PORTFOLIO *for pathogens in scope*

Comparatively small portfolio: At least 8 products: 3 antibacterial medicines; 5 antifungal medicines
On-patent medicines: 1 bedaquiline (Sirturo®)
Off-patent/generic medicines: 3 of 7 were selected for analysis** (itraconazole [F], levofloxacin [W], miconazole [F])
AWaRe medicines*:** 1 Watch group
Anti-TB medicines*:** 1

Pipeline for priority pathogens

Products on the market

PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT Evaluated: medicine & vaccine pipelines for priority** bacteria & fungi

A.1 Investments in R&D

Johnson & Johnson does not disclose publicly, or to the Benchmark, its R&D investments during 2019 and 2020 in antibacterial and antifungal medicines and/or vaccines for pathogens in scope. Johnson & Johnson has pledged USD 100 mn to the AMR Action Fund over the next ten years.

A.2.1 Medium-sized pipeline

The company has 14 projects targeting pathogens in scope: 12 medicines and two vaccines, all targeting bacterial pathogens. Out of the 14 projects, eight are in discovery stage, four are in preclinical stage, one is in clinical development and one received marketing approval during the period of analysis.

A.2.2 No clinical-stage novel medicines

Johnson & Johnson's clinical-stage medicine pipeline consists of one candidate, the paediatric adaptation of bedaquiline (Sirturo®). Johnson & Johnson does not currently have any medicine candidate that is considered novel in clinical development.

Pipeline targeting priority pathogens: 14† *As at 24 September 2021*

Discovery	Pre-clinical	Phase I	Phase II	Phase III	Approval
	♦ *S. aureus* vaccine			♦ Extraintestinal pathogenic *E. coli* vaccine (ExPEC9V)‡	Bedaquiline (Sirturo®) [*M. tuberculosis*] [FDA/Aug-19]: additional population: adolescent (12 - <18 years) [FDA/May-20]: additional population: paediatric (5 - <12 years)
				♦ Vaccine	

† Includes 11 confidential projects not shown in the figure.
‡ Progressed to Phase III after the end of the period of analysis.

**See Appendix V for information about eligibility for R&D projects and Appendix VII for eligibility criteria of products.
***Listed on the 2019 WHO EML.

A.2.3 Two vaccine candidates

Johnson & Johnson reports two vaccine projects in its pipeline. Its clinical-stage candidate, ExPEC9V is a Phase III vaccine targeting extraintestinal pathogenic *E. coli*. Johnson & Johnson also has a vaccine candidate against *S. aureus* in preclinical stage.

A.2.4 Candidates targeting critical and/or urgent priorities

Johnson & Johnson has projects targeting pathogens defined as 'critical' by WHO's list of priority pathogens and/or characterised as 'urgent' threats by the US Centers for Disease Control and Prevention (CDC). In clinical development, Johnson & Johnson has a vaccine candidate, ExPEC9V, that targets extraintestinal pathogenic *E. coli*. Johnson & Johnson also has projects that target *P. aeruginosa*.

A.3 Access and stewardship plans for late-stage projects

Johnson & Johnson has one vaccine (ExPEC9V) and one medicine in late-stage development [bedaquiline (Sirturo®)]. They are both covered by project-specific access plans.

The current stewardship activities ongoing for the adult indication of bedaquiline (Sirturo®) will extend to the new pediatric approval: for use in patients aged 5 - < 12 years and weighing at least 15 kg.

There are no clinical trials running in access countries[§] for the EXPEC9V vaccine, but Johnson & Johnson is planning to expand its Phase III trial to access countries.

B RESPONSIBLE MANUFACTURING Evaluated: antibacterials manufacturing (APIs and drug products)

B.1 Comprehensive environmental risk-management for own sites and suppliers; sets limits at own sites and suppliers

Johnson & Johnson reports a comprehensive strategy to minimise the environmental impact of wastewaters and solid waste generated from antibacterial manufacturing at its sites, including conducting audits every three years. It reports setting discharge limits in the receiving waters for all antibacterials manufactured at its sites, based on PNECs to limit AMR, as recommended by the AMR Industry Alliance. Johnson & Johnson also reports quantifying discharge levels at all its own sites using a mass balance approach, verified by chemical analysis if applicable.

Johnson & Johnson requires third-party suppliers of antibacterial APIs and drug products to follow the same standards, including limits based on PNECs. It reports conducting on-site audits of its suppliers typically every three years. Johnson & Johnson requests and reviews the discharge levels of its suppliers. It does not report how many suppliers have quantified discharge levels and are compliant with limits.

Johnson & Johnson expects external private waste-treatment plants to comply with its general environmental standards. Johnson & Johnson reports that it audits private waste-treatment plants based on risk and region. It also employs conservative measures for effluents sent to external public wastewater treatment plants.

B.2 Publicly discloses some information on environmental risk management

Johnson & Johnson publishes some components of its environmental risk-management strategy. It is a member of the AMR Industry Alliance, which publishes a list of recommended antibacterial discharge targets. It discloses that it has completed audits and an environmental risk assessment of all its pharmaceutical suppliers located in China and India, which also covers antibacterial discharge levels. Johnson & Johnson does not publish: (1) the results of environmental audits, conducted at its own sites, the sites of suppliers and/or external private and public waste-treatment plants; (2) a list of these suppliers and plants; or (3) the levels of antibacterial discharge from its own or suppliers' sites.

B.3 System in place to maintain production quality for own and suppliers' sites; no requests for official corrective action

Johnson & Johnson reports that its own sites and suppliers have a system to maintain high-quality antibacterial production, consistent with international GMP standards. This includes periodic risk-based audits and tracking of corrective and preventive actions. In general, Johnson & Johnson also requires its pharmaceutical suppliers to audit their own supplier sites based on risk. The Benchmark found no requests for official corrective action from the FDA or EMA related to non-conformities with cGMP at Johnson & Johnson's own sites or any subsidiaries that manufacture antibacterials.

C APPROPRIATE ACCESS & STEWARDSHIP – ACCESS

Evaluated: access activities relating to antibacterial & antifungal medicines & vaccines in 102 access countries[§]

Johnson & Johnson is not eligible for indicators: C.1.3 and C.2.3. For more information, see Appendix VII.

C.1.1 Filed to register on-patent medicines in 30 access countries

Johnson & Johnson performs above average, filing its one relevant on-patent medicine for registration in 30 access countries, including eight LICs. The medicine is the MDR-TB medicine bedaquiline (Sirturo®). Johnson & Johnson publicly discloses on its company's website where bedaquiline was filed for registration.

C.1.2 Filed to register off-patent/generic medicines in 29 access countries on average

Johnson & Johnson performs above average, filing all its three sample off-patent/generic medicines for registration in 29 access countries on average. All its three sample products are filed for registration in at least one LIC.

C.2.1 Several strategies to expand access to its on-patent medicine

Johnson & Johnson performs above average. It aims to expand access to its one relevant on-patent medicine in access countries through tenders, patient assistance programmes, access price settings and public or private partnerships. It collaborates with the GDF-Stop TB Partnership to provide 100 mg bedaquiline at a global access price of USD 340 per 6-month treatment course to GDF-eligible countries. The GDF-Stop TB Partnership also provides the paediatric formulation of bedaquiline (20 mg) at a price of USD 200 per 6-month treatment course. Johnson & Johnson provides evidence of patient reach and geographic reach for all its reported approaches. It publicly commits to providing its MDR-TB medicine to a cumulative 700,000 patients worldwide by 2025. Bedaquiline is available in all 30 WHO high-burden countries for MDR-TB.

C.2.2 Limited information on strategies to expand access to off-patent/generic medicines

Johnson & Johnson has an average performance. It has set equitable tiered-pricing principles and publicly states to apply equitable pricing policies to its antifungal itraconazole and antibiotic levofloxacin. Johnson & Johnson provides evidence of patient reach and geographic reach for two of its three relevant products in scope. Details were provided under the basis of confidentiality.

[§] 102 low- and middle-income countries where better access to medicine is most needed.

C.3 Several strategies to ensure continuous supply

Johnson & Johnson performs above average, with strategies reported in all four areas assessed. It ensures accurate demand planning and data sharing by forecasting demand of bedaquiline (Sirturo®) based on local tender patterns and utilisation trends in high burden MDR-TB countries, distributor demand forecasts and global donor grant budgeting cycles. It mitigates against shortage risks by keeping a buffer stock for APIs and finished products. Both bedaquiline API and finished product are manufactured in India with flexibility to scale production. It reports several capacity building or technology transfer initiatives including a technology transfer for the formulation, filling, and packaging processes of bedaquiline including with Pharmstandard (Russia). It mitigates substandard and falsified products by having a dedicated team. It uses packaging security features and digital technologies to detect illicit trade.

C APPROPRIATE ACCESS & STEWARDSHIP – STEWARDSHIP

Evaluated: stewardship activities relating to antibacterial & antifungal medicines globally

C.4 Comprehensive COI mitigation strategies in place for its educational programmes

Johnson & Johnson performs strongly in conflict of interest (COI) mitigation for the five AMR-related educational programmes for HCPs assessed by the Benchmark. To mitigate COI for all five programmes, it provides financial resources to independent third parties (The Union, the Chinese and Indonesian governments) to carry out the programme.

C.5 Engages in sales practices but does not engage in marketing practices to address appropriate use

Johnson & Johnson performs above average in sales practices. It does not deploy any sales agents to promote bedaquiline (Sirturo®) to healthcare professionals except in one country. However, for the remaining antibacterial and/or antifungal medicines it does not report whether it decouples incentives for sales agents from sales volumes to help prevent the inappropriate use of such medicines.

Johnson & Johnson does not engage in marketing practices that aim to address the appropriate use of its antibacterial and/or antifungal medicines as its marketing materials do not reflect emerging resistance trends or include treatment guidelines for healthcare professionals.

C.6 Makes two types of brochure and/or packaging adaptations to facilitate appropriate use by patients

Johnson & Johnson adapts brochures and packaging to facilitate the appropriate use of bedaquiline (Sirturo®) by patients. Johnson & Johnson performs well, taking account of language and adherence to treatment. It produces a package insert with information in four languages to streamline distribution. Further, it packaged a 6-month treatment regimen in a single bottle to facilitate patient adherence to treatment.

C.7 Active in one AMR surveillance programme; shares raw data in a restricted manner

Johnson & Johnson runs the multinational Drug Resistance Emergence Assessment in MDR-TB (DREAM) programme, which is focused on resistance against bedaquiline (Sirturo®) in 11 countries and has been running since 2015. Johnson & Johnson shares the raw data (from its clinical trials) through the Yale University Open Data Access (YODA) platform, which can only be accessed via approval through an independent scientific committee.

Overall Performance

2020 2021

49% 46%▼

Merck & Co, Inc (MSD)

Large R&D-based pharmaceutical company

Stock exchange: NYSE • Ticker: MRK • HQ: Kenilworth, NJ, US • Employees: 74,000

PERFORMANCE

MSD performs below average overall in its evaluated Research Areas compared to the other large research-based pharmaceutical companies in scope.

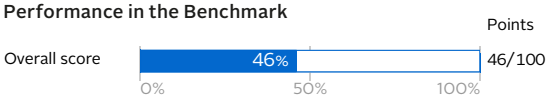
R&D: MSD is a middle-performing company in the R&D Research Area. Its 13-project pipeline has three vaccines. Three projects target critical and/or urgent pathogens. MSD has made a general commitment to expanding access to its products.

Responsible Manufacturing: Performs well. Reports environmental risk-management strategy for own sites and suppliers; quantifies discharge levels at own sites.

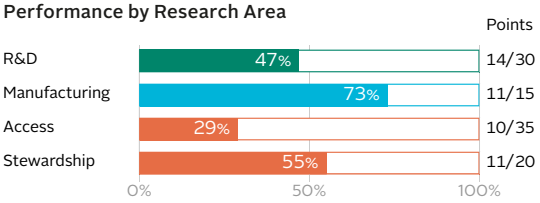
Appropriate Access: Performs less well. Discloses limited information on registration filings for its on- and off-patent products. Discloses some strategies to expand access and ensure continuous supply of its relevant product.

Stewardship: Middle-performing. It fully decouples incentives for sales agents from antibacterial sales volumes in the UK. It publicly shares aggregated results of its surveillance programmes. It reports broad conflict of interest mitigation for its educational programmes. It does not adapt brochures of packaging for patients.

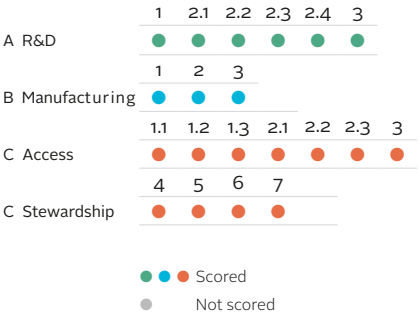
Performance in the Benchmark



Performance by Research Area



How Merck & Co was evaluated



OPPORTUNITIES FOR MSD

Develop and disclose project-specific plans to improve access and stewardship for R&D projects in late-stage development. MSD reports a commitment to expand access through broad registration, including in LMICs, and supports appropriate and responsible use of their antibacterial medicines. MSD can develop project-specific access and stewardship plans for all its late-stage R&D projects. For example, for its *S. pneumoniae* vaccine V116 it can commit to fast registration in countries with the highest burden of disease, and develop a pricing strategy that considers the ability to pay of target populations in those countries.

Expand its environmental risk-management strategy to suppliers and ensure compliance at all sites with antibacterial discharge limits by tracking and publicly disclosing progress and results. MSD reports to set limits and to quantify the discharge levels at its own sites. It can extend this practice to suppliers' sites and track compliance of both own and suppliers' sites with discharge limits and publicly disclose the results. To provide clear evidence of its progress, it can publicly report compliance at all sites. Disclosure of information, including the results of audits and antibacterial discharge levels of its own sites and suppliers' sites, is important. It can also publicly disclose the names and locations of its suppliers and waste-treatment plants for increased transparency.

Expand registration of medicines and vaccines to more access countries. MSD reports that ceftolozane/tazobactam (Zerbaxa®) was filed for registration in 25 access countries. It can file its antibacterial and antifungal medicines and vaccines (e.g. Zinplava™, Recarbio™ and Pneumovax 23®) in more countries, including low-income countries, with a high burden of disease. It can improve disclosure on where its medicines are registered and made available.

Fully decouple incentives for sales agents from sales volumes. MSD runs a pilot in the UK, in which it fully decouples incentives for sales agents from sales volumes of antibacterial medicines sold in UK hospitals. It can expand this practice to all countries it operates in and to all antibacterial and antifungal medicines.

Publicly share raw data from surveillance programmes. MSD runs multiple AMR surveillance programmes. It can publicly share raw data from these surveillance programmes: SMART, PACTS and STAR - anonymised and in a freely accessible format. Additionally, either MSD or the managing partners can publicly share raw data from the CANWARD and BSAC surveillance programmes.

CHANGES SINCE 2020

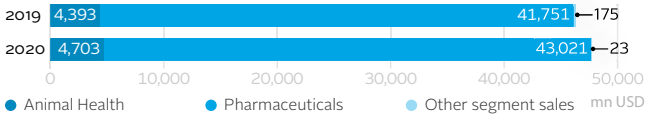
- In May 2020, MSD's technology and services provider ILUM Health Solutions combined with UPMC Infectious Disease Connect Inc. to share expertise and resources to enhance patient care, optimise antimicrobial therapy and reduce potential for drug resistance.
- In 2020, MSD expanded the functionality of the global SMART surveillance website, and it will put a mechanism in place for researchers to request access to anonymised raw data.

* All companies were assessed based on data submitted to the Benchmark in the current and previous periods of analysis, as well as information the companies have made publicly available, or that are accessible through other sources. For the 2021 Benchmark, MSD declined to submit data to the Antimicrobial Resistance Benchmark.

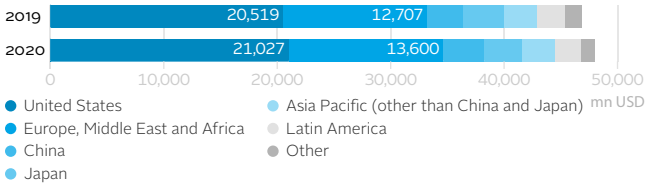
SALES AND OPERATIONS

Therapeutic areas: Cardiovascular, Diabetes, Hospital acute care, Immunology, Neuroscience, Oncology, Vaccines, Virology.
Business segments: Animal health, Pharmaceuticals
Product categories: Animal health, Innovative medicines, Vaccines
M&A since 2020: None in the antibacterial and/or antifungal sectors

Net sales by business segment



Net sales by region



PIPELINE *for pathogens in scope*

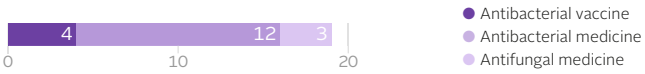
Pipeline size: 13 projects targeting pathogens in scope** (10 antibacterial medicines; 3 antibacterial vaccines).
Development stages: 2 clinical projects, including V116, a Phase II pneumococcal vaccine; and 7 discovery/preclinical projects.
Novelty: 0 novel clinical-stage medicine projects.
'Critical' and/or 'urgent' pathogens: 3 projects, relebactam/imipenem/cilastatin (Recarbrio™) targets carbapenem-resistant *Enterobacteriaceae*. It is active against *Klebsiella pneumoniae* carbapenemase (KPC), but not metallo-beta-lactamase (MBL)- producing *Enterobacteriaceae*. Fidaxomicin (Dificid®) targets *C. difficile*.
Regulatory approvals: 4 approvals. In July 2019, Relebactam/imipenem/cilastatin (Recarbrio™) was approved by the FDA for the treatment of complicated urinary tract infections (cUTI), including pyelonephritis, and complicated intra-abdominal infections (cIAI). In June 2020, Recarbrio™ received supplemental approval by the FDA for the treatment of hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP) in adults. In January 2020, Fidaxomicin (Dificid®) paediatric adaptation was approved by the FDA. In July 2021, Vaxneuvance™, pneumococcal conjugate vaccine (15-valent) was approved by the FDA.

PORTFOLIO *for pathogens in scope*

Comparatively small portfolio: At least 19 products: 12 antibacterial medicines; 4 antibacterial vaccines; 3 antifungal medicines
On-patent medicines: 6 (bezlotoxumab, ceftolozane/tazobactam, fidaxomicin, imipenem/cilastatin/relebactam, posaconazole, tedizolid)
On-patent vaccines: 3 (Liquid PedvaxHIB®, Pneumovax® 23, Vaxelis®)
Off-patent/generic medicines: 7 of 10 were selected for analysis** (benzathine benzylpenicillin [A], caspofungin [F], clotrimazole/betamethasone [F], daptomycin [R], ertapenem [W], gentamicin [A], moxifloxacin [W])
AWaRe medicines*:** 2 Access group; 4 Watch group; 2 Reserve group

Pipeline for priority pathogens

Products on the market



PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT Evaluated: medicine & vaccine pipelines for priority** bacteria & fungi

Pipeline targeting priority pathogens: 13 *As at 24 September 2021*

Discovery	Pre-clinical	Phase I	Phase II	Phase III	Approval
Protein synthesis inhibitor [*M. tuberculosis*]	♦ *Shigella spp.* vaccine		♦ *S. pneumoniae* vaccine adult (V116)	Sivextro® - additional population: paediatric [Gram positive bacteria]	♦ *S. pneumoniae* vaccine (Vaxneuvance™) [FDA/Jul-21]†
Partnership with Orchid Pharma, India - Bacteria & fungi	Compound screening ALIS (MOA) [*M. tuberculosis*]				Fidaxomicin (Dificid®) [*C. difficile*] [FDA: Jan-20]: additional population: paediatric
	ATP synthase inhibitor 1 mo GLP safety studies [*M. tuberculosis*]				Relebactam/imipenem/cilastatin (Recarbrio™) [*Enterobacteriaceae*] [FDA/Jul-19] cUTI, including pyelonephritis and cIAI
	In vivo preclinical PK/PD dose ranging project [*M. tuberculosis*]				[FDA/Jun-20] HABP/VABP
	Diarylquinoline (TBAJ-587) [*M. tuberculosis*]				

♦ = Vaccine
GLP = Good Laboratory practice
PK/PD = Pharmacokinetic/pharmacodynamic
cUTI = Complicated urinary tract infection
cIAI = Complicated intra-abdominal infection
HABP = Hospital-acquired bacterial pneumonia
VABP = Ventilator-associated bacterial pneumonia
† Approved after the end of the period of analysis.

** See Appendix V for information about eligibility for R&D projects and Appendix VII for eligibility criteria of products.
*** Listed on the 2019 WHO EML.

A.1 Investments in R&D

MSD does not disclose publicly, or to the Benchmark, its R&D investments during 2019 and 2020 in antibacterial and antifungal medicines and/or vaccines for pathogens in scope. MSD has pledged USD 100 mn to the AMR Action Fund over the next ten years.

A.2.1 Medium-sized pipeline

The company has 13 projects targeting pathogens in scope: 10 medicines and three vaccines, all targeting bacterial pathogens. Out of the 13 projects, two are in discovery stage, five are in preclinical development, two are in clinical development and four received marketing approval.

A.2.2 MSD extending indications for their antibacterials

MSD's clinical-stage medicine pipeline consists of both innovative and adaptive R&D projects. Relebactam/imipenem/cilastatin (Recarbrio™) received first marketing approval in July 2019 from the FDA for the treatment of complicated urinary tract (cUTI) and intra-abdominal infections (IAI). Recarbrio™ does not meet any of WHO's innovativeness criteria. MSD has three adaptive projects aiming, respectively, to extend the indications of fidaxomicin (Dificid®), relebactam/imipenem/cilastatin (Recarbrio™) and tedizolid (Sivextro®).

A.2.3 Three vaccine candidates

MSD reports three vaccine projects in its pipeline. It includes one innovative candidate in preclinical development targeting *Shigella spp.* and two adaptive vaccine candidates targeting *S. pneumoniae:* V114 and V116.

A.2.4 Two candidates targeting critical and/or urgent priorities

MSD has two medicines in its R&D pipeline targeting pathogens defined as 'critical' by WHO's list of priority pathogens and/or characterised as 'urgent' threats by the US Centers for Disease Control and Prevention (CDC). Relebactam/imipenem/cilastatin (Recarbrio™) targets carbapenem-resistant *Enterobacteriaceae*, and fidaxomicin (Dificid®) targets C. *difficile*.

A.3 General commitments towards expanding access and affordability practices

MSD does not report any specific access or stewardship plans for any of its six late-stage medicine and vaccine projects targeting pathogens in scope. Four out of six projects have ongoing clinical trials in access countries.‡ The company has made a general commitment about registering its products in LMICs, expanding access through broad registration and improving affordability. MSD supports the appropriate and responsible use of its antibacterial and antifungal medicines by supporting hospitals globally to strengthen their AMS programmes.

B RESPONSIBLE MANUFACTURING Evaluated: antibacterials manufacturing (APIs and drug products)

B.1 Environmental risk-management for own sites and suppliers; sets limits at own sites and suppliers

MSD reports a strategy to minimise the environmental impact of wastewaters and solid waste from antibacterial manufacturing at its sites, including audits at least every 1-2 years. It reports setting discharge limits in the receiving environment for all antibacterials manufactured at its sites, based on PNECs to limit AMR, as recommended the AMR Industry Alliance. It also reports quantifying discharge levels but there is no information on the methods used and compliance with set limits.

MSD requires third-party suppliers of antibacterials to follow similar standards, including on-site audits and limits based on PNECs. There is limited information whether it requests and reviews the discharge levels of its suppliers.

MSD expects external private waste-treatment plants to comply with its general environmental standards. It reports auditing external private and public waste-treatment plants but no details on audit parameters are provided. It also does not report whether conservative measures for effluents sent to external public wastewater plants are employed.

B.2 Publicly discloses some information on environmental risk management and commitment to setting limits

MSD publishes some components of its environmental risk-management strategy. It is a member of the AMR Industry Alliance, which publishes a list of recommended antibacterial discharge targets. MSD publishes its commitment to setting these targets. It does not publish: (1) the results of environmental audits, whether conducted at its own sites, the sites of suppliers or external private and public waste-treatment plants; (2) a list of these suppliers and plants; or (3) the levels of antibacterial discharge from its own or suppliers' sites.

B.3 System in place to maintain production quality for own and suppliers' sites; no requests for official corrective action

MSD reports that its own sites and suppliers have a system to maintain high-quality antibacterial production, consistent with international GMP standards. This includes risk-based internal audits and tracking of corrective and preventive actions. It also requires its suppliers to audit their own suppliers. The Benchmark found no requests for official corrective action from the FDA or EMA related to non-conformities with cGMP at MSD's own sites or any subsidiaries that manufacture antibacterials.

C APPROPRIATE ACCESS & STEWARDSHIP – ACCESS

Evaluated: access activities relating to antibacterial & antifungal medicines & vaccines in 102 access countries‡

C.1.1 Limited information on registration filings for on-patent medicines

MSD performs below average as it does not disclose where it has filed five of its six relevant on-patent medicines for registration. However, it publicly reports that its on-patent medicine, ceftolozane/tazobactam (Zerbaxa®), a reserve antibiotic used to treat intra-abdominal infections, acute pyelonephritis, cUTIs and hospital-acquired pneumonia, was filed for registration in 25 LMICs.

C.1.2 Limited information on registration filings for off-patent/generic medicines

MSD's performance is low. It reports no evidence of filing its seven relevant off-patent/generic medicines for registration in access countries.

C.1.3 No information on registration filings for on-patent vaccines

MSD reports no evidence of filing its three relevant on-patent vaccines for registration in access countries.

C.2.1 Limited information on strategies to expand access to on-patent medicines

MSD performs below average. It expands access to its on-patent medicines in access countries through differential pricing and public or private partnerships and publicly commits not to enforce patents in low-income countries. MSD does not provide evidence of patient reach and geographic reach in low- and middle-income countries.

C.2.2 Limited information on strategies to expand access to off-patent/generic medicines

MSD's performance is low as it discloses limited information on how it expands access to its seven relevant off-patent/generic medicines. It publicly reports to expand access through differential pricing and public or private partnerships with governments, NGOs and distribution channels. MSD does not provide evidence of patient reach and geographic reach.

‡ 102 low- and middle-income countries where better access to medicine is most needed.

C.2.3 Limited information on strategies to expand access to on-patent vaccines

MSD performs below average as it discloses limited information on how its expands access to its on-patent vaccines in access countries. It publicly discloses having differential pricing and intellectual property policies, and participating in public or private partnerships. To set the price of its vaccines, MSD takes into account the level of economic development, the channel of distribution and the public health needs. It has inter- and intra-country pricing strategies to allow for price flexibility. MSD publicly commits not to enforce patents in low-income countries. MSD does not provide evidence of patient reach and geographic reach for its strategies.

C.3 Limited information on strategies to ensure continuous supply

MSD has an average performance. It publicly reports to ensure accurate demand planning and commits to maintaining a reliable supply of its medicines and vaccines. MSD has supply agreements with local manufacturing partners to allow for local production of its vaccine. To mitigate against substandard and falsified products, MSD uses security features, has a dedicated anti-counterfeiting team in place, and raises public awareness.

C APPROPRIATE ACCESS & STEWARDSHIP – STEWARDSHIP

Evaluated: stewardship activities relating to antibacterial & antifungal medicines globally

C.4 Broad COI mitigation strategies in place for its educational programmes

MSD performs well in the analysis of its top five AMR-related educational programmes for healthcare professionals in conflict of interest (COI) mitigation. To mitigate COI for three programmes, it provides financial resources to independent third parties (CIDEIM, BSAC and the University of Dundee) to develop the programme. One programme (developed by the company) has all three COI mitigation strategies looked for by the Benchmark: (1) content is developed by a third party independent from the company's own marketing department; (2) participants are not provided financial or material incentives (as it is a website); and (3) it does not use branded materials. The remaining programme has one COI mitigation strategy: it is unclear whether content is developed independently from its marketing department or whether it uses branded materials.

C.5 Engages in sales and marketing practices to address appropriate use

MSD performs above average in sales practices. It started a pilot in 2019 where it does not reward its sales agents based on antibacterial volumes sold in UK hospitals. However, outside of this pilot MSD does not report whether it decouples incentives for sales agents from sales volumes to help prevent the inappropriate use of its antibacterial and/or antifungal medicines.

MSD engages in marketing practices that aim to address the appropriate use of its antibacterial and/or antifungal medicines. Its marketing materials reflect emerging resistance trends and/or include treatment guidelines for healthcare professionals: it has developed its Star of Stewardship principles in which all marketing materials must include, e.g. specific indications, treatment duration and dose.

C.6 Does not report adapting brochures and/or packaging to facilitate appropriate use by patients

MSD does not report adapting brochures and/or packaging to facilitate the appropriate use of its antibacterial and/or antifungal medicines by patients.

C.7 Active in multiple AMR surveillance programmes; openly publishes aggregated results

MSD is active in multiple AMR surveillance programmes. It runs the multinational SMART programme, which is focused on respiratory infections and complicated intra-abdominal and urinary tract infections in 63 countries and has been running since 2002. MSD only shares the aggregated results through peer-reviewed open-access journal articles as well as on the online SMART database, a restricted data platform. Additionally, it is planning to make anonymised source data available for researchers upon request through the SMART database. For the remaining programmes, only the aggregated results are shared through peer-reviewed open-access journal articles, as well as on an open-access data platform for the CANWARD programme (a national programme managed by the Canadian Antimicrobial Resistance Alliance).

Overall Performance

2020 2021

54% 63%▲

Novartis AG

Large R&D-based pharmaceutical company

Stock exchange: SWX • Ticker: NOVN • HQ: Basel, Switzerland • Employees: 105,794

PERFORMANCE

Novartis performs above average overall in its evaluated Research Areas compared to the other large research-based pharmaceutical companies in scope.

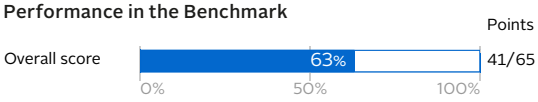
R&D: Novartis no longer carries out R&D projects that target pathogens in scope of the AMR Benchmark.

Responsible Manufacturing: Performs strongly. Reports comprehensive environmental risk-management strategy for own sites and suppliers; co-leads in reporting compliance with limits at own sites, audits external private and public waste-treatment plants.

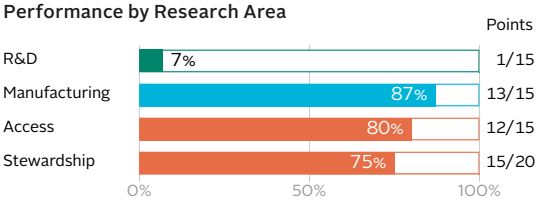
Appropriate Access: Performs strongly. Files some of its relevant products (on- and off-patent products) for registration in access countries. Reports several strategies to expand access and ensure continuous supply of its relevant products.

Stewardship: Performs well. It decouples sales incentives for a significant portion of its sales by using tenders. It supports a surveillance programme in Poland of which aggregated results are publicly shared. It reports comprehensive conflict of interest mitigation for its educational programmes. It adapts brochures for patients.

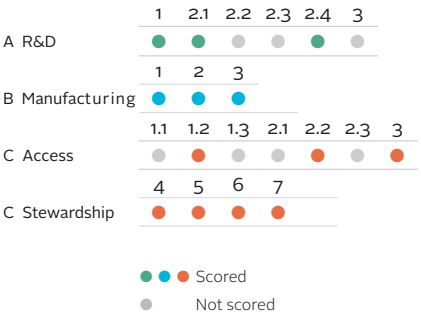
Performance in the Benchmark



Performance by Research Area



How Novartis was evaluated



OPPORTUNITIES FOR NOVARTIS

Engage in antibacterial and antifungal R&D including medicines and vaccines against priority pathogens. Novartis contributes to the AMR Action Fund, a joint venture that aims to bring 2-4 new antibiotics to the market by 2030 and has a partnership with GARDP to provide antibiotic formulations accessible for children with drug-resistant infections. Novartis can engage in in-house R&D, through acquisition or collaboration with other companies, or by joining existing public private partnerships, to target resistant pathogens for which R&D is limited, such as *Campylobacter* spp. and *H. pylori*.

Ensure compliance to antibacterial discharge limits at suppliers sites by tracking and publicly disclosing progress and results specific to antibacterials for all sites. Novartis can expand its requirements to quantify discharge levels as it does for its own sites to all its suppliers' sites and track compliance with set limits. It can publicly disclose the results including the discharge levels. The company currently publishes information on compliance at own sites with pharmaceutical limits that include, but is not specific to, antibacterials. Novartis can also apply limits directly in effluent to fully mitigate AMR risk.

Expand registration and ensure availability of antibacterial and antifungal medicines. Novartis can expand registration of its antibiotics and antifungals listed on the 2021 WHO EML, such as daptomycin and tigecycline, to more countries, including low-income countries, with a high burden of disease.

Fully decouple incentives for sales agents from sales volumes. In Novartis' limited promotional activities directed at healthcare professionals, it links part of its sales agents' incentives to sales volumes of antibacterial and antifungal medicines. It can fully decouple such incentives for sales agents.

Publicly share raw data from surveillance programme. Novartis supports the national Diagnostics of Central Nervous System Bacterial Infections (KOROUN) programme, which is managed by the Polish National Medicines Institute. Either Novartis or the managing partner can publicly share raw data from this surveillance programme.

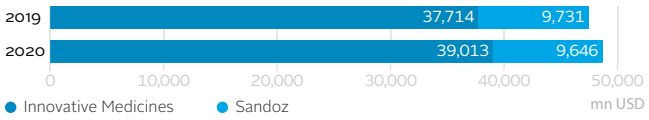
CHANGES SINCE 2020

- Approval secured of a OneNovartis AMR program to minimise spread of AMR by focusing efforts where the company can make a difference. The programme prioritises appropriate access, responsible manufacturing and responsible use. The initiative was launched in May 2021.
- In July 2020, Sandoz and the Austrian government formed a public-private partnership to increase production capacity at Sandoz's antibiotics manufacturing site in Kundl, Austria. Sandoz commits to investing more than USD 175 mn over the next five years to new antibiotics manufacturing technology.
- Novartis has expanded registration of its sample off patent/generic medicines to more access countries, meeting the opportunity provided in the 2020 Benchmark.
- Since 2019, Novartis supports the Diagnostics of Central Nervous System Bacterial Infections (KOROUN) study, a national AMR surveillance programme focused on community-acquired respiratory tract infections in Poland. Before this programme Novartis was not involved in AMR surveillance.

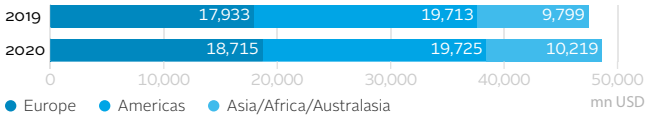
SALES AND OPERATIONS

Therapeutic areas: Cardiovascular, renal and metabolism; Immunology, hepatology and dermatology; Neuroscience; Oncology; Ophthalmology; Respiratory.
Business segments: Innovative Medicines, Sandoz
Product categories: Biosimilars, Generic medicines, Innovative medicines
M&A since 2020: In February 2021, Novartis division Sandoz signed an agreement to acquire GSK's cephalosporin antibiotic business for USD 350 mn in addition to milestone payments up to USD 150 mn.

Net sales by business segment



Net sales by region



PIPELINE *for pathogens in scope*

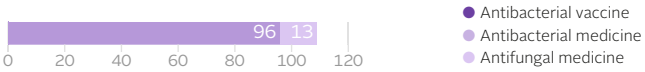
Novartis is currently not developing any projects targeting the pathogens in scope*.

PORTFOLIO *for pathogens in scope*

Comparatively large portfolio: At least 109 products: 96 antibacterial medicines; 13 antifungal medicines
Off-patent/generic medicines: 10 of 109 were selected for analysis* (amoxicillin [A], amoxicillin/clavulanic acid [A], clarithromycin [W], daptomycin [R], itraconazole [F], levofloxacin [W], linezolid [T], rifampicin [T], tigecycline [R], voriconazole [F])
AWaRe medicines:** 21 Access group; 35 Watch group; 2 Reserve group
Anti-TB medicines:** 9

Pipeline for priority pathogens

Products on the market



PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT Evaluated: medicine & vaccine pipelines for priority* bacteria & fungi

A.1 Investments in R&D
Novartis did not report investments during 2019 and 2020 in R&D for antibacterial and antifungal medicines and/or vaccines for pathogens in scope. Novartis has pledged an unknown amount to the AMR Action Fund over the next 10 years.

A.2.1 Novartis does not engage in R&D for products in scope
The company does not report any project in its pipeline targeting pathogens in scope.

A.2.2 Novelty of pipeline
Novartis is not eligible for this indicator as it does not have any R&D candidates in clinical development.

A.2.3 Not active in vaccine development
Novartis is not active in vaccine development targeting pathogens in scope.

A.2.4 Critical and/or urgent priorities
Novartis is not eligible for this indicator as it does not have any R&D candidates in development.

A.3 Access and stewardship planning
Novartis is not eligible for this indicator as it has no projects targeting pathogens in scope in late-stage clinical development.
Companies are expected to have plans in place for pipeline projects in Phase II and beyond.

Pipeline targeting priority pathogens: 0 *As at 24 September 2021*

Novartis is currently not developing any projects targeting the pathogens in scope.*

* See Appendix V for information about eligibility for R&D projects and Appendix VII for eligibility criteria of products.
** Listed on the 2019 WHO EML.

B RESPONSIBLE MANUFACTURING Evaluated: antibacterials manufacturing (APIs and drug products)

B.1 Comprehensive environmental risk-management for own sites and suppliers; audits external private and public waste-treatment plants

Novartis reports a comprehensive strategy to minimise the environmental impact of wastewaters and solid waste from antibacterial manufacturing at its sites, including audits every 2-4 years. It reports setting discharge limits in the receiving environment for all antibacterials manufactured at its sites, based on PNECs to limit AMR, as recommended by the AMR Industry Alliance. Discharge levels are quantified at all sites using a mass balance approach or chemical analysis, as applicable. It reports that compliance of own sites with discharge limits is tracked. It also publicly reports that 80% of its own sites are compliant with discharge limits for pharmaceuticals which include, but are not specific to, antibacterials.

Novartis requires third-party suppliers of antibacterials to follow the same standards, including limits based on PNECs. It reports conducting on-site audits every three years. It requests and reviews the discharge levels of its suppliers. It is undisclosed how many of the 160 supplier sites report to have quantified discharge levels.

Novartis expects external private waste-treatment plants to comply with its general environmental standards. It audits external private and public waste-treatment plants at least every three years, based on risk. It requests external private and public wastewater treatment plants to provide dilution and flow rate data to inform the mass balance approach and employs conservative measures when needed.

B.2 Publicly discloses some information on environmental risk management and compliance with limits for pharmaceuticals including antibacterials

Novartis publishes some components of its environmental risk-management strategy. It is a member of the AMR Industry Alliance, which publishes a list of recommended antibacterial discharge targets. Novartis publishes its commitment to setting discharge limits, at own and suppliers' sites, for pharmaceuticals in the environment which include but go beyond antibacterials. It publicly discloses that 80% of its own sites are compliant to these general limits. The discharge levels themselves are not published. Novartis also does not publish: (1) the results of environmental audits, conducted at its own sites, the sites of suppliers and/or external private and public waste-treatment plants; or (2) a list of these suppliers and plants.

B.3 System in place to maintain production quality for own and suppliers' sites; no requests for official corrective action

Novartis reports that its own sites and suppliers have a system to maintain high-quality antibacterial production consistent with international GMP standards. This includes periodic risk-based audits and tracking of corrective and preventive actions. Novartis also requires its suppliers to audit their own suppliers. The Benchmark found no requests for official corrective action from the FDA or EMA related to non-conformities with cGMP at Novartis' own sites or any subsidiaries that manufacture antibacterials.

C APPROPRIATE ACCESS & STEWARDSHIP – ACCESS

Evaluated: access activities relating to antibacterial & antifungal medicines & vaccines in 102 access countries***

Novartis is not eligible for indicators: C.1.1, C.1.3, C.2.1 and C.2.3. For more information, see Appendix VII.

C.1.2 Filed to register off-patent/generic medicines in 30 access countries on average

Novartis performs above average, filing nine of its 10 relevant off-patent/generic medicines for registration in 30 access countries on average. Its most widely filed relevant product is amoxicillin/clavulanic acid, filed in 70 access countries. Three of its relevant products are filed in less than ten access countries. Six of its relevant products are filed for registration in at least one LIC.

C.2.2 Several strategies to expand access to off-patent/generic medicines

Novartis performs above average, with access strategies reported for four of its ten relevant off-patent/generic medicines. It aims to expand access to its off-patent/generic medicines in access countries through equitable pricing, tenders and competitive prices. It provides evidence of patient reach and geographic reach for all its reported approaches. Novartis Access pricing policy ranges the prices from USD 1 per treatment per month or at tailored prices. Novartis Sub-Saharan African (SSA) Unit takes a high-volume, lower-price approach to increase the patient reach. Novartis has set public goals to increase the patient reach twofold by 2022 and fivefold by 2025 through its SSA unit. In 2020, Novartis, through its Sandoz division, committed to sell some of its medicines, of which antibiotics used to treat patients with COVID-19-related symptoms, at zero-profit to governments in up to 79 eligible low-income and lower-middle-income countries.

C.3 Several strategies to ensure continuous supply

Novartis performs above average, with strategies reported in all four areas assessed. Novartis ensures accurate demand planning and data sharing by following a monthly rolling process from one to 36 months in advance and ensures weekly data sharing for anti-infectives. Novartis mitigates against shortage risks by keeping buffer stocks for key starting materials, drug substance and drug products. It ensures dual sourcing when possible. It has set daily, weekly, and monthly KPIs to monitor its supply chain performance. Novartis reports one technology transfer initiative in Pakistan, to locally produce its penicillin portfolio. To mitigate against substandard and falsified products, Novartis monitors online platforms, uses data analytics, spectrometry technologies, anticounterfeiting packaging features and mobile applications.

*** 102 low- and middle-income countries where better access to medicine is most needed.

C APPROPRIATE ACCESS & STEWARDSHIP – STEWARDSHIP

Evaluated: stewardship activities relating to antibacterial & antifungal medicines globally

C.4 Comprehensive COI mitigation strategies in place for its educational programmes

Novartis performs strongly in conflict of interest (COI) mitigation for the five AMR-related educational programmes for HCPs assessed by the Benchmark. To mitigate COI for one programme, it provides financial resources to an independent third party (MedShr) to develop the programme. The remaining four programmes have all three COI mitigation strategies looked for by the Benchmark: (1) content is developed independently from its marketing department; (2) a pledge not to provide financial or material incentives to participants; and (3) it does not use branded materials.

C.5 Engages in sales and marketing practices to address appropriate use

Novartis performs above average in sales practices. It reports that it sells a significant portion of its antibacterial and/or antifungal medicines through tenders and does not have sales incentives linked to the sales volume of these tenders. Outside of these tenders, promotion of antibacterial and/or antifungal medicines is limited and the focus of such promotional activities is not on these medicines.

Novartis engages in marketing practices that aim to address the appropriate use of its antibacterial and/or antifungal medicines. Its marketing materials include emerging resistance trends and/or include treatment guidelines for healthcare professionals: for azithromycin, cefixime, amoxicillin/clavulanic acid and cefpodoxime by including antimicrobial stewardship guidelines for healthcare professionals and by combining the most recent information from WHO's AWaRe categorisation with information on resistance closely aligned with national guidelines for its top ten global antibacterial medicines.

C.6 Makes one type of brochure and/or packaging adaptation to facilitate appropriate use by patients

Novartis adapts brochures to facilitate the appropriate use of amoxicillin/clavulanic acid by patients. Novartis is middle-performing in this measure, taking account of paediatric use. It has created paediatric guidance for amoxicillin/clavulanic acid that focuses on correct dosing for children.

C.7 Active in one AMR surveillance programme; openly publishes aggregated results

Novartis is active in the national Diagnostics of Central Nervous System Bacterial Infections (KOROUN) programme, which is managed by the Polish National Medicines Institute with support from Novartis and has been running since 2019. It is focused on community-acquired respiratory tract infections in Poland. Only the aggregated results are shared through open-access journal articles and the KOROUN website.

Overall Performance

2020 2021

52% 57% ▲

Otsuka Pharmaceutical Co, Ltd

Large R&D-based pharmaceutical company

Stock exchange: TSE • Ticker: 4578 • HQ: Tokyo, Japan • Employees: 5,657

PERFORMANCE

Otsuka performs average overall in its evaluated Research Areas compared to the other large research-based pharmaceutical companies in scope.

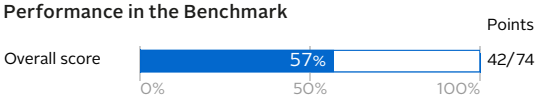
R&D: Otsuka performs well in R&D. All four projects in its pipeline are antibacterial medicines: three targeting *M. tuberculosis* and one targeting a critical and/or urgent pathogen (*P. aeruginosa*). It has one novel antituberculosis candidate in clinical development. Otsuka has two projects in late-stage development with comprehensive plans for access and stewardship.

Responsible Manufacturing: Performs low. Reports a general environmental risk-management strategy but without a specific aim to limit AMR.

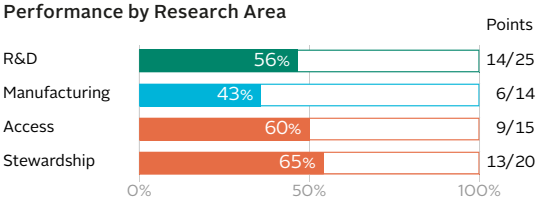
Appropriate Access: Middle-performing. Files its relevant products (on-patent medicine) for registration in access countries. Reports some strategies to expand access and ensure continuous supply of its relevant product.

Stewardship: Middle-performing. It does not promote delamanid (Deltyba®) to healthcare professionals which is its only product in scope. It is not involved in AMR surveillance programmes. It reports comprehensive conflict of interest mitigation for its educational programme. It adapts brochures for patients.

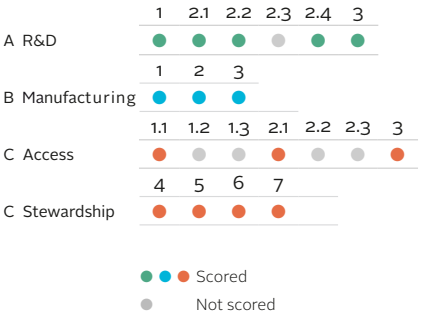
Performance in the Benchmark



Performance by Research Area



How Otsuka was evaluated



OPPORTUNITIES FOR OTSUKA

Expand breadth of R&D pipeline into more pathogens. Despite being the smallest of the large R&D-based companies assessed in the AMR Benchmark, Otsuka optimises its resources and has achieved remarkable expertise in tuberculosis R&D, being one of the main investors in TB R&D worldwide. Otsuka can now redirect this expertise and invest in innovative in-house R&D to target resistant pathogens for which R&D is limited, such as *Campylobacter* spp. and *H. pylori*, through acquisition or collaboration with other companies, or by joining existing public private partnerships.

Develop an AMR-specific environmental risk-management strategy and increase public disclosure. Otsuka reports a commitment to manufacture its products in an environmentally responsible manner without specifying whether AMR is taken into account. The company can develop an AMR strategy for its own manufacturing sites, the sites of suppliers and external private waste-treatment plants, based on the guidelines of the AMR Industry Alliance, of which Otsuka is a member. This includes setting limits and quantifying discharge levels to track compliance. Moreover, Otsuka can publish information on how it manages environmental risk related to antibacterial manufacturing to curb AMR.

Ensure availability and affordability of delamanid (Deltyba®). Otsuka can expand the availability of delamanid (Deltyba®) by filing for registration in more access countries, including through its voluntary licensing agreement with Viatris, in particular in the 30 countries with the highest MDR-TB burden identified by the WHO.

Engage in AMR surveillance activities. Otsuka is not active in AMR surveillance activities. It can engage in AMR surveillance programmes through setting up (in-house) programmes or by funding established programmes run by research organisations. Additionally, Otsuka should publicly share raw data collected from the programme.

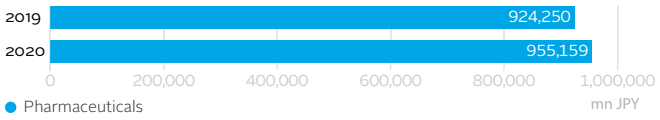
CHANGES SINCE 2020

- In February 2020, Otsuka joined the Project to Accelerate New Treatments for Tuberculosis (PAN-TB), a collaboration among philanthropic, non-profit and private sectors partners that aims to develop an investigational drug regimen capable of treating all forms of TB.
- In September 2020, the European Medicines Agency (EMA) approved the extension of Otsuka's MDR-TB treatment delamanid (Deltyba®) to include children with a body weight of at least 30 kg. In July 2021, the EMA approved the use of the 25 mg dispersible tablet formulation of delamanid (Deltyba®) for the treatment of pulmonary MDR-TB in adults, adolescents, children and infants with a body weight of at least 10 kg.

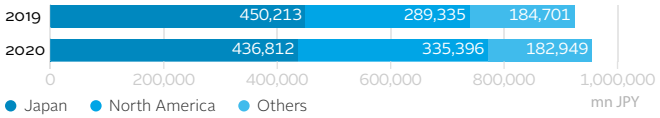
SALES AND OPERATIONS

Therapeutic areas: Cardiovascular and renal diseases, Central nervous system, Oncology, Ophthalmology, Tuberculosis
Business segments: Pharmaceuticals
Product categories: Innovative medicines
M&A since 2020: None in the antibacterial and/or antifungal sectors

Revenue by business segment



Revenue by region



PIPELINE *for pathogens in scope*

Pipeline size: 4 projects targeting pathogens in scope* (4 antibacterial medicines).
Development stages: 1 clinical project, OPC-167832, a Phase II candidate for the treatment of *M. tuberculosis*; and 1 preclinical project targeting *P. aeruginosa*.
Novelty: 1 novel project, OPC-167832, an antituberculosis candidate that meets all four criteria set by WHO for innovativeness.
'Critical' and/or 'urgent' pathogens: 1 project, VIS705, a preclinical therapeutic candidate, targeting *P. aeruginosa*, including MDR strains.
Regulatory approvals: 2 approvals. Marketing authorisation by the EMA was granted to the antituberculosis drug delamanid (Deltyba®) for the treatment of children with a body weight of at least 30 kg. In July 2021 the EMA approved the use of the 25 mg dispersible tablet formulation of delamanid (Deltyba®) for the treatment of pulmonary MDR-TB in adults, adolescents, children and infants with a body weight of at least 10 kg.

PORTFOLIO *for pathogens in scope*

Comparatively small portfolio: At least 1 product: 1 antibacterial medicine
On-patent medicine: 1 (delamanid)
AWaRe medicines: 0
Anti-TB medicine:** 1

Pipeline for priority pathogens

Products on the market

PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT Evaluated: medicine & vaccine pipelines for priority* bacteria & fungi

A.1 Investments in R&D
Otsuka discloses to the Benchmark its R&D investments during 2019 and 2020 in antibacterial and antifungal medicines and/or vaccines for pathogens in scope. Otsuka reports that it invested USD 34.61 mn in R&D for antibacterial medicines in 2019 and 2020. This constitutes a small proportion of its revenues compared to the other companies who reported investments to the Benchmark.

A.2.1 Pipeline targets mainly *M. tuberculosis*
The company reports four projects targeting pathogens in scope. All of them are medicines targeting bacterial pathogens: three are antituberculosis agents and the remaining one targets *P. aeruginosa*. Out of the four projects, one is in preclinical stage, one in Phase II, delamanid (Deltyba®) for paediatric patients received marketing approval during the period of analysis and the adult indication remains in Phase IV.

A.2.2 Small innovative pipeline
Otsuka's clinical-stage medicine pipeline consists of both innovative and adaptive R&D projects. Otsuka has one antituberculosis medicine candidate which meets all four WHO's innovativeness criteria: OPC-167832. In September 2020, EMA approved the extension of Otsuka's MDR-TB treatment delamanid (Deltyba®) to include children with a body weight of at least 30 kg. In July 2021, the EMA approved the use of the 25 mg dispersible tablet formulation of delamanid (Deltyba®) for the treatment of pulmonary MDR-TB in adults, adolescents, children and infants with a body weight of at least 10 kg.

A.2.3 Not active in vaccine development
Otsuka is not active in vaccine development tar-

Pipeline targeting priority pathogens: 4* *As at 24 September 2021*

Discovery	Pre-clinical	Phase I	Phase II	Phase III	Approval
	VIS705 [*P. aeruginosa*]		OPC-167832 [*M. tuberculosis*]		Delamanid (Deltyba®) [*M. tuberculosis*] [EMA/Sep-20] additional population: paediatric (>30 kg) [EMA/Jul-21] additional formulation (25mg) (>10 kg)†

*** Includes 1 Phase IV project not shown in the figure.
† Approved after the end of the period of analysis.

* See Appendix V for information about eligibility for R&D projects and Appendix VII for eligibility criteria of products.
** Listed on the 2019 WHO EML.

geting pathogens in scope.

A.2.4 One candidate targeting critical and/or urgent priorities

Otsuka has one medicine candidate in its R&D pipeline targeting pathogens defined as 'critical' by WHO's list of priority pathogens and/or characterised as 'urgent' threats by the US Centers for Disease Control and Prevention (CDC). VIS705 is in preclinical development and targets *P. aeruginosa*, including MDR strains.

A.3 Comprehensive planning for access and stewardship

Otsuka has two medicine projects in late-stage development. For its project OPC-167832, in Phase II, Otsuka has committed itself contractually to a comprehensive access strategy as stipulated by the Bill & Melinda Gates Foundation. Otsuka also reports plans to engage in surveillance and monitoring of the emergence of resistance to this new antituberculosis candidate.

For the paediatric indication of the antituberculosis drug delamanid (Deltyba®) for which marketing authorisation by the EMA was granted in September 2020 for children above 30 kg and on July 2021 for children above 10 kg, Otsuka also has comprehensive strategies to ensure its appropriate use, as well as availability and affordability in access countries†.

B RESPONSIBLE MANUFACTURING Evaluated: antibacterials manufacturing (APIs and drug products)

B.1 No AMR-specific environmental risk management strategy

Otsuka's general environmental strategy includes a commitment to manufacture its products in an environmentally responsible manner but without a specific aim to limit AMR. Its strategy also does not include any actions specific to delamanid (Deltyba®), the only antibacterial produced at its manufacturing sites, in both its API and drug product forms.

Otsuka does not report making any requirements in this regard to the third-party drug product manufacturer contracted for an intermediate step in delamanid production.

There is also limited information on the requirements Otsuka makes of external private waste-treatment plants, in terms of strategy, audits and discharge limits and levels. It reports these plants are audited every three years but audit parameters are not related to AMR. It also reports wastewater is treated on-site and external private and public wastewater treatment plants are not used.

B.2 Publicly discloses some information on environmental risk management

Otsuka publishes some components of its environmental risk-management strategy, without specific references to AMR. It is a member of the AMR Industry Alliance, which publishes a list of recommended antibacterial discharge targets. Otsuka does not publish: (1) the results of environmental audits, whether conducted at its own sites, the sites of suppliers or external private and public waste-treatment plants; (2) a list of these suppliers and plants; or (3) the levels of antibacterial discharge from its own or suppliers' sites.

B.3 System in place to maintain production quality for own and suppliers' sites; no requests for official corrective action

Otsuka reports that its own sites and suppliers have a system to maintain high-quality antibacterial production consistent with international GMP standards. This includes periodic risk-based audits and tracking of corrective and preventive actions. Otsuka reports it does not have any subsuppliers of antibacterials. The Benchmark found no requests for official corrective action from the FDA or EMA related to non-conformities with cGMP at Otsuka's own sites or any subsidiaries.

C APPROPRIATE ACCESS & STEWARDSHIP – ACCESS

Evaluated: access activities relating to antibacterial & antifungal medicines & vaccines in 102 access countries†

Otsuka is not eligible for indicators: C.1.2, C.1.3, C.2.2 and C.2.3. For more information, see Appendix VII.

C.1.1 Filed to register its on-patent medicine in 9 access countries

Otsuka has an average performance, filing its one on-patent medicine for registration in nine access countries. The medicine is the anti-tuberculosis medicine, delamanid (Deltyba®).

C.2.1 Some strategies to expand access to its on-patent medicine

Otsuka has an average performance. It aims to expands access to its one on-patent medicine in access countries through a voluntary licensing agreement and a partnership. It partners with the Global Drug Facility - Stop TB Partnership to provide delamanid at a global access price of USD 1,700 for a 6-month treatment course. Otsuka has a voluntary licensing agreement with Viatris and R-Pharm to accelerate access to delamanid (Deltyba®) in high TB burden countries. Otsuka and Viatris have entered into a technology transfer agreement, to produce and distribute a lower-cost generic version of delamanid (Deltyba®). Otsuka provides evidence of patient reach and geographic reach for its reported approaches. It estimates that at least 24,700 treatment courses were distributed in 2020. Delamanid (Deltyba®) is available in all 30 WHO high-burden countries for MDR-TB.

C.3 Some strategies to ensure continuous supply

Otsuka has an average performance, with strategies reported in all four areas assessed. Otsuka ensures accurate demand planning and data sharing by conducting long-term planning and S&OP planning. Otsuka mitigates against shortage risks by keeping a 1,5-year average buffer stock in the countries where delamanid (Deltyba®) has a marketing authorisation. It conducts annual inventory checks and external audits of its stocks. Otsuka conducts a technology transfer to allow Viatris to manufacture, package, and distribute delamanid (Deltyba®) in a set of access countries. To mitigate against substandard and falsified products, Otsuka uses security features such as serialisation, GS1 barcodes and GDSN traceability. Delamanid (Deltyba®) has a unique packaging process including alu-alu blisters, tamper-proof seals, and unique identifier codes.

† 102 low- and middle-income countries where better access to medicine is most needed.

C APPROPRIATE ACCESS & STEWARDSHIP – STEWARDSHIP

Evaluated: stewardship activities relating to antibacterial & antifungal medicines globally

C.4 Comprehensive COI mitigation strategies in place for its educational programme

Otsuka performs strongly in conflict of interest (COI) mitigation for the one AMR-related educational programme for HCPs assessed by the Benchmark. The programme has all three COI mitigation strategies looked for by the Benchmark: (1) content is developed independently from its marketing department; (2) a pledge not to provide financial or material incentives to participants; and (3) it does not use branded materials.

C.5 Does not promote its antibacterial medicine

Otsuka performs strongly in sales practices as it does not promote its product in scope. It does not deploy any sales agents to promote delamanid (Deltyba®) to healthcare professionals, because treatment is only available in specialised centres under tightly controlled conditions. Since Otsuka does not develop or use marketing materials for delamanid (Deltyba®) to promote it to healthcare professionals, the company is not eligible to be assessed on marketing materials.

C.6 Makes one type of brochure and/or packaging adaptation to facilitate appropriate use by patients

Otsuka adapts brochures to facilitate the appropriate use of delamanid (Deltyba®) by patients. Otsuka is middle-performing in this measure, taking account of language. It has translated its Educational Risk Minimisation Materials into English, French, Spanish and Russian, which are distributed through the Global Drug Facility.

C.7 No involvement in AMR surveillance programmes

Otsuka is the only large R&D-based company that does not report any involvement in AMR surveillance programmes.

Overall Performance

2020 2021

69% **81%** ▲

Pfizer Inc

Large R&D-based pharmaceutical company

Stock exchange: NYSE • Ticker: PFE • HQ: New York, NY, United States • Employees: 78,500

PERFORMANCE

Pfizer performs well overall in its evaluated Research Areas compared to the other large research-based pharmaceutical companies in scope.

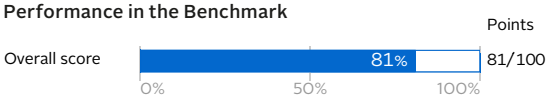
R&D: Pfizer performs strongly in R&D. Its 13-project pipeline includes five vaccines. Seven of its projects target critical and/or urgent pathogens. It has a novel antifungal in clinical development. Pfizer reports access and stewardship plans for all eight of its late-stage projects.

Responsible Manufacturing: Performs strongly. Reports comprehensive environmental risk-management strategy for own sites and suppliers; quantifies discharge levels at all its own and supplier sites.

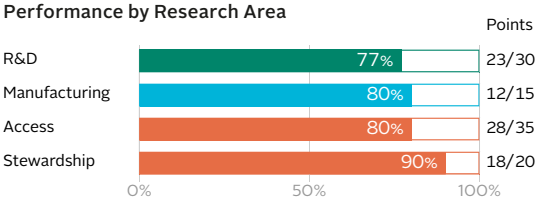
Appropriate Access: Performs strongly. Files some of its on-off-patent products for registration in access countries. Reports several strategies to expand access and ensure continuous supply of its relevant products.

Stewardship: Is the leader. It publicly shares raw data of its ATLAS surveillance programme. It fully decouples incentives for sales agents from antibacterial sales volumes in the UK. It reports comprehensive conflict of interest mitigation for its educational programmes. It adapts packaging for patients.

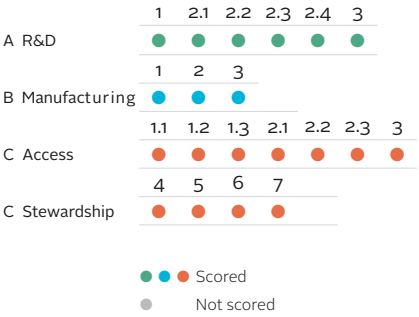
Performance in the Benchmark



Performance by Research Area



How Pfizer was evaluated



OPPORTUNITIES FOR PFIZER

Fully decouple incentives for sales agents from sales volumes. Pfizer fully decouples incentives for sales agents from sales volumes of antibacterial medicines in the UK. It can expand this practice to all countries it operates in and to all antibacterial and antifungal medicines.

Expand breadth of R&D pipeline into more pathogens. Pfizer has the largest late-stage clinical pipeline compared to peers in the AMR Benchmark. It has made a series of acquisitions of small biotech companies to increase the size of its pipeline. Pfizer can expand the focus of its pipeline to target resistant pathogens for which R&D is limited, such as *Campylobacter* spp. and *H. pylori*.

Ensure compliance with antibacterial discharge limits at suppliers' sites by tracking and publicly disclosing progress and results specific to antibacterials for all sites. Pfizer tracks the compliance of all own sites with set discharge limits. It can also track such compliance of all its suppliers' sites since Pfizer reports all suppliers have quantified discharge levels and it can publicly disclose the results. The company currently publishes information on compliance of own and suppliers' sites with the guidelines of the AMR Industry Alliance but it is unclear whether this includes compliance to discharge limits.

Expand registration of Trumenba® and NeisVac-C®. Pfizer can file its vaccines Trumenba® and NeisVac-C® for registration in more countries, including low-income countries with a high burden of disease.

Expand accessibility of its antibacterial and antifungal medicines in access countries. Pfizer can implement new programmes and partnerships to expand access to its antibacterial and antifungal medicines in access countries while demonstrating how it improves the availability and affordability of its medicines, including in low-income countries. For example, it can expand access to Zavicefta® and Zinforo® in Sub-Saharan Africa while taking ability-to-pay into account.

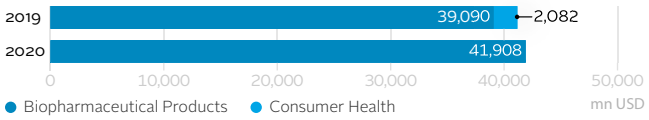
CHANGES SINCE 2020

- In February 2021, BSAC, the European Bank for Reconstruction and Development, EBRD, and Pfizer co-created a global digital learning network for HCPs addressing AMR, antimicrobial stewardship (AMS), and COVID's impact on AMR and pandemic planning.
- Pfizer is addressing antimicrobial stewardship health disparities through multiple efforts. As part of its efforts, Pfizer and the Wellcome Trust launched the Surveillance Partnership to Improve Data for Action on Antimicrobial Resistance (SPIDAAR) in July 2020, which is a new collaboration with the governments of Ghana, Kenya, Malawi and Uganda to track resistance patterns and better understand the burden of AMR in LMICs.
- Pfizer purchased shares of ContraFect's common stock for approximately USD 3 mn. ContraFect intends to use the capital to fund its R&D activities, including a Phase III candidate targeting *S. aureus*.
- In the last year, Pfizer acquired Arixa Pharmaceuticals and Amplyx Pharmaceuticals, Inc., two companies focused on developing antibacterial and antifungal treatments, respectively.

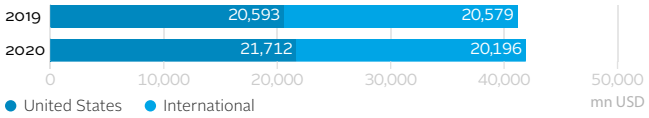
SALES AND OPERATIONS

Therapeutic areas: Hospital, Inflammation & immunology, Internal medicine, Oncology, Rare diseases, Vaccines
Business segments: Biopharmaceutical products
Product categories: Biosimilars, Generic medicines, Innovative medicines, Vaccines
M&A since 2020: In July 2019, Pfizer and GSK combined their consumer health care business into a joint venture, with Pfizer controlling an equity interest of 32%. In November 2020, Pfizer spun its Upjohn Business off to combine it with Mylan N.V. to form Viatris Inc. In October 2020, Pfizer acquired Arixa Pharmaceuticals, a company focused on developing next-generation oral antibiotics for drug-resistant Gram-negative infections. In April 2021, Pfizer acquired Amplyx Pharmaceuticals, Inc., including their lead drug fosmanogepix, a potentially first-in-class antifungal treatment.

Revenue by business segment



Revenue by region



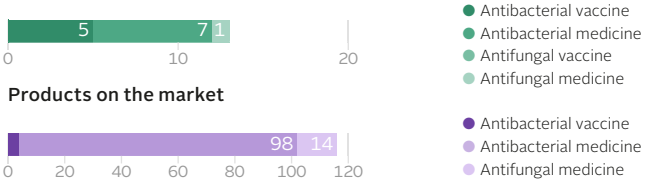
PIPELINE *for pathogens in scope*

Pipeline size: 13 projects targeting pathogens in scope* (7 antibacterial medicines; 5 antibacterial vaccines; 1 antifungal medicine).
Development stages: 6 clinical projects, including a Phase III vaccine candidate for *C. difficile* infections and a Phase II clinical vaccine candidate for the prevention of group B *Streptococcus* infections; and 5 discovery/pre-clinical projects.
Novelty: 1 project, potential first-in-class Phase II antifungal: fosmanogepix.
'Critical' and/or 'urgent' pathogens: 7 projects, with the focus on resistant *Enterobacteriaceae, C. auris* and *C. difficile*. Pfizer has a Phase III vaccine candidate for *C. difficile*. Its Phase II antifungal fosmanogepix targets *C. auris*.
Regulatory approvals: 4 approvals. In September 2019, the FDA gave a supplemental approval for ceftaroline fosamil (Teflaro®/Zinforo®)** to treat Acute Bacterial Skin and Skin Structure Infections (ABSSSI) in neonatal populations (from birth to less than 2 months of age). In June 2021, the FDA approved Prevnar20™, a pneumococcal 20-valent conjugate vaccine for adults. Avycaz®/Zavicefta®** received two label extensions by the EMA in October 2020.

PORTFOLIO *for pathogens in scope*

Comparatively large portfolio: At least 116 products: 98 antibacterial medicines; 4 antibacterial vaccines; 14 antifungal medicines
On-patent medicines: 5 (anidulafungin, ceftazidime/avibactam, ceftaroline, isavuconazole, tavaborole)
On-patent vaccines: 4 (Trumenba®, NeisVac-C®, Nimenrix®, Prevnar 13®)
Off-patent/generic medicines: 10 of 107 were selected for analysis* (amoxicillin [A], azithromycin [W], chloramphenicol [A], ethambutol/isoniazid/pyrazinamide/rifampicin [T], ethambutol/isoniazid/rifampicin [T], fluconazole [F], minocycline [W], polymyxin b [R], tigecycline [R], voriconazole [F])
AWaRe medicines*:** 26 Access group; 31 Watch group; 8 Reserve group
Anti-TB medicines*:** 11

Pipeline for priority pathogens



Products on the market

PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT Evaluated: medicine & vaccine pipelines for priority* bacteria & fungi

A.1 Investments in R&D
Pfizer does not disclose publicly, or to the Benchmark, its R&D investments during 2019 and 2020 in antibacterial and antifungal medicines and/or vaccines for pathogens in scope. Pfizer has pledged USD 100 mn to the AMR Action Fund over the next ten years.

A.2.1 Pfizer nearly doubles the size of its pipeline
The company reports 13 projects targeting pathogens in scope: eight medicines and five vac-

Pipeline targeting priority pathogens: 13† *As at 24 September 2021*

Discovery	Pre-clinical	Phase I	Phase II	Phase III	Approval
			Ceftazidime/avibactam (Avycaz®/Zavicefta®)** [*Enterobacteriaceae, P. aeruginosa*] - additional population: neonates	♦ *C. difficile* vaccine (PF-06425090)	♦ *S. pneumoniae* 20-valent conjugate vaccine (Prevnar20™) [FDA/Jun-21]‡
			♦ Group B *Streptococcus* vaccine (PF-06760805)	Aztreonam/avibactam (PF-06947387) [*Enterobacteriaceae*]	Ceftaroline fosamil (Teflaro®/Zinforo®)** [*S. aureus*] [FDA/Sep-19] additional population: neonates
			Fosmanogepix [*C. auris*]	♦ *S. pneumoniae* 20-valent conjugate vaccine (Prevnar20™) - additional population: paediatric	

♦ = Vaccine

† Includes 5 confidential projects not shown in the figure.
‡ Approved after the end of the period of analysis.

* See Appendix V for information about eligibility for R&D projects and Appendix VII for eligibility criteria of products.

** Avycaz® and Teflaro® are marketed by Allergan in the USA.
*** Listed on the 2019 WHO EML.

cines. Twelve targeting bacterial pathogens and one targets fungal pathogens. Out of the 13 projects, five are in discovery/preclinical stage, six are in clinical development and two received marketing approval.

A.2.2 Both innovative and adaptive medicine clinical candidates

Pfizer's clinical-stage medicine pipeline consists of both innovative and adaptive R&D projects. Pfizer is working on extending the indications of ceftazidime/avibactam (Avycaz®/Zavicefta®)** and ceftaroline fosamil (Teflaro®/Zinforo®).** It is developing the combination of aztreonam/avibactam (PF-06947387) against MDR gram-negative infections. In April 2021, Pfizer acquired Amplyx Pharmaceuticals Inc and is now taking over the clinical development of its novel antifungal, fosmanogepix.

A.2.3 Five vaccine candidates

Pfizer reports five vaccine projects in its pipeline. It includes three innovative and two adaptive projects. Pfizer's vaccines in clinical stages of development include candidates targeting *C. difficile*, group B *Streptococcus* and *S. pneumoniae*. In June 2021 Prevnar20™, a 20-valent pneumococcal vaccine was approved by the FDA. Pfizer is conducting Phase III trials to extend the use of this newly approved vaccine to paediatric populations.

A.2.4 Seven candidates targeting critical and/or urgent priorities

Pfizer has seven projects targeting pathogens defined as 'critical' by WHO's list of priority pathogens and/or characterised as 'urgent' threats by the US Centers for Disease Control and Prevention (CDC). In clinical development, Pfizer has medicine candidates against Carbapenem-resistant/ESBL-producing *E. coli* and *C. auris*, and a vaccine candidate targeting *C. difficile*.

A.3 Comprehensive planning for access and stewardship

Pfizer has eight late-stage R&D projects targeting pathogens in scope, the highest number across all the R&D-based companies evaluated, four of them are vaccines. Three are in Phase II, three in Phase III and two have obtained marketing approval.

For seven out of eight of its projects in late-stage development, Pfizer has ongoing clinical trials or aims to file the successful products in access countries[§]. The plans for this projects include a wide range of access components such as filing for registration in access countries[§], equitable pricing and measures to strengthen supply. Furthermore, its late-stage R&D medicine projects are covered by portfolio-wide stewardship plans, including initiatives for surveillance (ATLAS) and research and education on AMR (via unrestricted grants). For its recently acquired Phase II antifungal, fosmanogepix, Pfizer plans to continue the Expanded Access Programme that Amplyx Pharmaceuticals Inc had in place.

B RESPONSIBLE MANUFACTURING Evaluated: antibacterials manufacturing (APIs and drug products)

B.1 Comprehensive environmental risk-management for own sites and suppliers; tracks compliance with limits at own sites

Pfizer reports a comprehensive strategy to minimise the environmental impact of wastewaters and solid waste from antibacterial manufacturing at its sites, including audits every three years. It reports setting discharge limits in the receiving environment for all antibacterials manufactured at its sites, based on PNECs to limit AMR, as recommended by the AMR Industry Alliance. Discharge levels are quantified at all sites using a mass balance approach, verified by chemical analysis if applicable. It reports that compliance of own sites with discharge limits is tracked.

Pfizer requires third-party suppliers of antibacterials to follow the same standards, including limits based on PNECs. It reports conducting on-site audits at least every five years. It requests and reviews the discharge levels of its suppliers. All supplier sites have quantified discharge levels.

Pfizer expects external private waste-treatment plants to comply with its general environmental standards. It audits these plants every 3-6 years which includes the suitability of technologies used for processing waste and protocols for preventing contamination. It also employs conservative measures for effluents sent to external private and public wastewater treatment plants.

B.2 Publicly discloses some information on environmental risk management and commitment to set limits

Pfizer publishes some components of its environmental risk-management strategy. It is a member of the AMR Industry Alliance, which publishes a list of recommended antibacterial discharge targets. Pfizer publishes its commitment to setting these targets. It also publicly discloses that it is developing a, AMR Industry Alliance sponsored, consensus-based standard to demonstrate responsible manufacturing of antibiotics. Pfizer publicly discloses that >90% of own sites are compliant with the guidelines of the AMR Industry Alliance, and that >80% suppliers are assessed against these guidelines. It is unclear whether such compliance also includes compliance with discharge limits. Pfizer does not publish: (1) the results of environmental audits, conducted at its own sites, the sites of suppliers and/or external private and public waste-treatment plants; (2) a list of these suppliers and plants; or (3) the levels of antibacterial discharge from its own or suppliers' sites.

B.3 System in place to maintain production quality for own and suppliers' sites; no requests for official corrective action

Pfizer reports that its own sites and suppliers have a system to maintain high-quality antibacterial production consistent with international GMP standards. This includes periodic risk-based audits and tracking of corrective and preventive actions. Pfizer also requires its suppliers to audit their own suppliers. The Benchmark found no requests for official corrective action from the FDA or EMA related to non-conformities with cGMP at Pfizer's own sites or any subsidiaries that manufacture antibacterials.

C APPROPRIATE ACCESS & STEWARDSHIP – ACCESS

Evaluated: access activities relating to antibacterial & antifungal medicines & vaccines in 102 access countries[§]

C.1.1 Filed to register on-patent medicines in 14 access countries on average

Pfizer performs above average, filing four of its five relevant on-patent medicines for registration in 14 access countries[§] on average. Its most widely filed relevant product is the antifungal anidulafungin (Eraxis; Ecalta®) used to treat invasive candidiasis, filed in 22 access countries. Its reserve antibiotic, ceftazidime/avibactam (Zavicefta®), was filed for registration in 20 access countries, including three LICs. Its antifungal isavuconazole (Cresemba®) was filed for registration in nine access countries.

C.1.2 Filed to register off-patent/generic medicines in 17 access countries on average

Pfizer performs above average, filing eight of ten relevant off-patent/generic medicines for reg-

** Avycaz® and Teflaro® are marketed by Allergan in the USA.

§ 102 low- and middle-income countries where better access to medicine is most needed.

istration in 17 access countries on average. Its most widely filed relevant product is the antifungal fluconazole, filed in 52 access countries. Six of its sample products are filed in less than 10 access countries. Four of its sample products are filed for registration in at least one LIC.

C.1.3 Filed to register on-patent vaccines in 24 access countries on average

Pfizer has an average performance, filing three of its four relevant on-patent vaccines for registration in access countries. Its most widely filed relevant vaccine is the Pneumococcal Conjugate Vaccine (13-valent) (Prevnar 13®) filed in 65 access countries. Prevnar 13® is followed by the meningococcal vaccine Nimenrix® , filed for registration in 23 access countries, including LICs.

C.2.1 Several strategies to expand access to on-patent medicines

Pfizer performs above average, with access strategies reported for three of five relevant on-patent medicines. It aims to expand access to its on-patent medicines in access countries through equitable pricing policies, one price per patient capitation model, and patient assistance programmes. To set the prices of ceftazidime/avibactam (Zavicefta™) and isavuconazole (Cresemba®), Pfizer takes into account local economic conditions, the average income, and GDP growth. It allows for net price flexibility for specific procurement requests. Pfizer provides evidence of patient reach and geographic reach for all its reported approaches. It estimates to have ensured access to ceftaroline (Zinforo®) ceftazidime/avibactam (Zavicefta™) and isavuconazole (Cresemba®) for 51,000 cumulative patients in low- and middle-income countries in 2020.

C.2.2 Several strategies to expand access to off-patent/generic medicines

Pfizer performs above average, with access strategies reported for four of its ten relevant off-patent/generic medicines. It aims to expand access in low- and middle-income countries through donations and public/private partnerships. It provides evidence of patient and geographic reach for all its reported approaches. Pfizer takes part in the International Trachoma Initiative (ITI) and donated 31 mn azithromycin treatments to 12 countries in 2020. It extended its donation programme until 2025. Through its Diflucan® Partnership Program, Pfizer distributed 7mn doses of fluconazole to nine access countries through governments and NGOs in 2019 and 2020.

C.2.3 Several strategies to expand access to on-patent vaccines

Pfizer performs above average, with access strategies reported for one of its four relevant on-patent vaccines. It aims to expand access in access countries through equitable tiered pricing, public/private partnerships, humanitarian emergency assistance settings and tenders. It has set a six-tiered pricing policy for Prevnar 13®. The tiers are defined by several criteria such as countries' GNI per capita. Pfizer partners with Gavi to provide Pneumococcal Conjugate Vaccine (13-valent) (Prevnar 13®) to Gavi-eligible and Gavi-transitioned countries at a public price of USD 2.90 per dose until 2027. Pfizer provides evidence of patient reach and geographic reach for all its reported approaches. It commits to supply 930 mn doses of its Pneumococcal Conjugate Vaccine (13-valent) (Prevnar 13®) by 2027 through its partnership with Gavi.

C.3 Several strategies to ensure continuous supply

Pfizer performs above average, with strategies reported in all four areas assessed. Pfizer ensures accurate demand planning and data analytics by forecasting on a monthly and 24-month rolling basis. Pfizer mitigates against shortage risks by keeping buffer stocks for its finished products at country-level, for APIs at a global-level, and manufactures some of its APIs in-house. Pfizer reports one technology transfer initiative. Since 2014, it has engaged in a public/private partnership in South Africa to enable a local partner to manufacture Pneumococcal Conjugate Vaccine (13-valent) (Prevnar 13®). To mitigate against substandard and falsified products, Pfizer maintains a Disruption Programme which identifies and disrupts online illicit sales. Pfizer uses serialisation with unique products identifiers and has a public counterfeit awareness page.

C APPROPRIATE ACCESS & STEWARDSHIP – STEWARDSHIP

Evaluated: stewardship activities relating to antibacterial & antifungal medicines globally

C.4 Comprehensive COI mitigation strategies in place for its educational programmes

Pfizer performs strongly in conflict of interest (COI) mitigation for the five AMR-related educational programmes for HCPs assessed by the Benchmark. To mitigate COI for all five programmes, it provides financial resources to independent third parties (BSAC, the University of Dundee, EBRD, ISID and Micron) to develop the programme.

C.5 Engages in sales and marketing practices to address appropriate use

Pfizer performs above average in sales practices. It reports that it partly decouples incentives for sales agents from sales volumes of its antibacterial and/or antifungal medicines. Its percentage of variable pay is capped at 30% and sales targets are set at the national level. Its incentives for sales agents in emerging markets in Asia are provided on the basis of confidentiality. However, Pfizer does not reward its sales agents based on antibacterial volumes sold in the UK.

Pfizer engages in marketing practices that aim to address the appropriate use of its antibacterial and/or antifungal medicines consistent with the approved indication. Its marketing materials reflect emerging resistance trends and/or include treatment guidelines for healthcare professionals: for all antibacterial medicines and isavuconazole (Cresemba®), by using data from its ATLAS surveillance programme in the materials.

C.6 Makes three types of brochure and/or packaging adaptations to facilitate appropriate use by patients

Pfizer adapts packaging to facilitate the appropriate use of azithromycin (Zithromax®) by patients. Pfizer performs strongly in this measure, taking account of adherence to treatment, paediatric use and language. It adapts the packaging of azithromycin, named the Z-Pak, which facilitates patient adherence by organising the pill intake for each day, so that the patient knows exactly which pill(s) to take on which day until the Z-Pak is completed. Moreover, Pfizer includes a QR code on the packaging of azithromycin as an oral suspension that directs patients to a video explaining how to administer the oral suspension properly for adults and children. This is applied in Vietnam and the Philippines and the video will be played in the local language. Finally, Pfizer has translated instructions on the packaging to the local language in Japan.

C.7 Active in multiple AMR surveillance programmes; one openly shares raw data

Pfizer leads in this area. It is active in multiple AMR surveillance programmes. It runs the multinational ATLAS programme, which is focused on resistance against its antibacterial and antifungal medicines in 81 countries and has been running since 2004. Pfizer shares the raw data on the AMR Register, an open-access data platform, as well as the aggregated results on the ATLAS website and through peer-reviewed open-access journal articles. For the remaining programmes, only the aggregated results are shared through peer-reviewed open-access journal articles, as well as on open-access data platforms for the SENTRY programme (an antifungal resistance programme managed by JMI laboratories) and the CANWARD programme (a national programme managed by the Canadian Antimicrobial Resistance Alliance).

Overall Performance

2020 2021

42% 60%▲

Sanofi

Large R&D-based pharmaceutical company

Stock exchange: EPA • Ticker: SAN • HQ: Paris, France • Employees: 99,412

PERFORMANCE

Sanofi performs average overall in its evaluated Research Areas compared to the other large research-based pharmaceutical companies in scope.

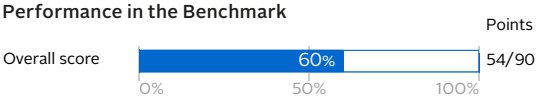
R&D: Sanofi performs less well in the R&D Research Area. Its six-project pipeline has three vaccines and three medicines. No project targets critical and/or urgent pathogens. Sanofi has four projects in late-stage development for which it reports having access plans.

Responsible Manufacturing: Performs well. Reports environmental risk-management strategy for own sites and suppliers; quantifies discharge levels at all own sites

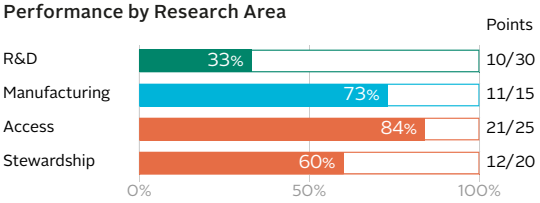
Appropriate Access: Performs strongly. Files its on-and off-patent products for registration in access countries. Reports several strategies to expand access and ensure continuous supply of its relevant products.

Stewardship: Middle-performing. It does not promote antibacterial and/or antifungal medicines to healthcare professionals outside France. It supports a surveillance programme in France of which aggregated results are publicly shared. It reports comprehensive conflict of interest mitigation for its educational programme. It does not adapt brochures or packaging for patients.

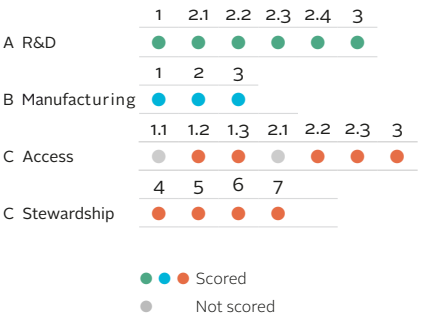
Performance in the Benchmark



Performance by Research Area



How Sanofi was evaluated



OPPORTUNITIES FOR SANOFI

Expand breadth of R&D pipeline into more pathogens. Sanofi has antibacterial vaccines and medicines in late-stage clinical development that target, e.g., *S. pneumonia* and *M. tuberculosis*. Sanofi can expand the focus of its pipeline to target resistant pathogens for which R&D is limited, such as *Campylobacter* spp. and *H. pylori*. It can do so by investing in in-house R&D, through acquisition or collaboration with other companies, or by joining existing public private partnerships.

Expand and tailor access and stewardship plans for late-stage R&D projects. Sanofi has both vaccines and medicines in late-stage clinical development. It can improve access to these new products, by developing plans for registration, affordability and sustainable supply. For example, for their phase II vaccine, Skypac, Sanofi can develop equitable pricing plans that consider ability-to-pay and apply supply chain best practices including buffer and safety stocks and shortage mitigation strategies. In addition, Sanofi can expand its stewardship plans for its medicine R&D projects by getting involved in comprehensive surveillance activities resistance trends information to their products as well as other medicines often given alongside them in the long multidrug treatments required for this disease, and to do it in relevant geographical regions where limited evidence is available.

Ensure compliance with antibacterial discharge limits at suppliers' sites by tracking and publicly disclosing progress and results specific to antibacterials for all sites. Sanofi can quantify discharge levels at all suppliers' sites and track compliance with set limits, as it does at own sites, and publicly disclose the results. To provide clear evidence of its progress it can publicly report compliance at all sites. Disclosure of information, including the results of audits and antibacterial discharge levels of its own sites and suppliers' sites, is important. It can also publicly disclose the names and locations of its suppliers and waste-treatment plants for increased transparency.

Expand registration of antibacterial and antifungal medicines. Sanofi can expand filing for registration of its off-patent antibiotics and antifungals listed on the 2021 WHO EML, such as colistin and fosfomycin, to more countries, including low-income countries, with a high burden of disease.

Publicly share raw data from surveillance programme. Sanofi supports a national programme focused on *S. pneumoniae*, the Observatoires Régionaux du Pneumocoque (ORP) programme, managed by the National Reference Centre for Pneumococci (NRCP). Either Sanofi or the NRCP can publicly share raw data from this surveillance programme.

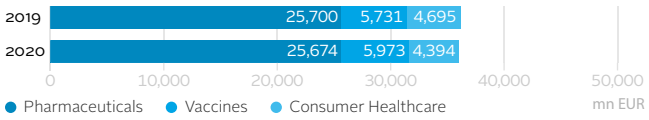
CHANGES SINCE 2020

- Since 2020, Sanofi reports requesting its suppliers to conduct risk assessments according to the guidelines of the AMR Industry Alliance including quantification of discharge levels against limits.
- In November 2019, Sanofi and Cyclamed launched the AnTRIbiotics campaign, which encourages the general public to bring expired or unused antibiotics back to the pharmacy.

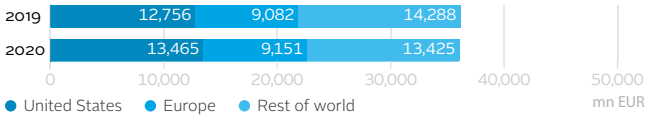
SALES AND OPERATIONS

Therapeutic areas: Cardiovascular diseases, Diabetes, Infectious diseases, Inflammatory & immune diseases, Oncology, Rare Diseases & Rare Blood disorders, Neurology.
Business segments: Pharmaceuticals, Vaccines, Consumer healthcare
Product categories: Consumer health products, Generic medicines, Innovative medicines, Vaccines
M&A since 2020: None in the antibacterial and/or antifungal sectors

Net sales by business segment



Net sales by region



PIPELINE *for pathogens in scope*

Pipeline size: 6 projects targeting pathogens in scope* (3 antibacterial medicines; 3 antibacterial vaccines).
Development stages: 4 clinical projects, including the Phase II pneumococcal conjugate vaccine (Skypac) candidate; and Shan6™, a Phase III hexavalent vaccine targeting among others *H. influenzae* and *B. pertussis*, for which Sanofi has already obtained marketing authorisation.
Novelty: 0 novel clinical-stage medicine projects.
'Critical' and/or 'urgent' pathogens: 0 projects targeting 'critical' and/or 'urgent' pathogens.
Regulatory approvals: 1 approval. In May 2021 the Indian regulatory authorities approved Shan6™, a paediatric hexavalent vaccine targeting *H. influenzae* and *B. pertussis*.

PORTFOLIO *for pathogens in scope*

Mid-sized portfolio: At least 47 products: 33 antibacterial medicines; 11 antibacterial vaccines; 3 antifungal medicines
On-patent vaccines: 3 (Hexaxim®, Menactra®, Shan5™)
Off-patent/generic medicines: 10 of 44 were selected for analysis* (amoxicillin [A], cefotaxime [W], ceftriaxone [W], clotrimazole [F], colistin [R], Fosfomycin [R], isoniazid [T], metronidazole [A], nystatin [F], rifampicin [T])
AWaRe medicines:** 7 Access group; 14 Watch group; 2 Reserve group
Anti-TB medicines:** 7

Pipeline for priority pathogens

Products on the market

PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT Evaluated: medicine & vaccine pipelines for priority* bacteria & fungi

A.1 Investments in R&D

Sanofi reports to the Benchmark the amount invested during 2019 and 2020 in R&D for antibacterial and antifungal medicines and/or vaccines for pathogens in scope. Specific investment figures were provided under confidentiality. As a proportion of its revenues, Sanofi reports lower R&D investments than other companies assessed in this indicator. In absolute terms, however, the amount it invests is the second largest.

A.2.1 Small pipeline

The company reports six projects targeting pathogens in scope: three medicines and three vaccines, all targeting bacterial pathogens. Out of the six projects, three are in clinical development and one received marketing approval.

A.2.2 No clinical-stage novel projects

Sanofi's clinical-stage medicine pipeline consists of two adaptive projects developing formulations and optimising treatment regimens for antituberculosis medicines. A new water dispersible formulation of rifapentine/isoniazid for improved dosing in latent tuberculosis in children is in Phase II. In Phase III, rifapentine is included in a trial aiming at optimising the treatment of latent and active tuberculosis with a shorter and simpler dosing regimen.

A.2.3 Three vaccine candidates

Sanofi reports three vaccine projects in its pipeline. It includes one innovative candidate in

Pipeline targeting priority pathogens: 6* ** *As at 24 September 2021*

Discovery	Pre-clinical	Phase I	Phase II	Phase III	Approval
			♦ *S. pneumonia* (conjugate) vaccine (Skypac) Rifapentine/isoniazid - additional formulation: fixed-dose water-dispersible tablet for paediatric patients [*M. tuberculosis*]	Rifapentine - New regimen: shorter treatment [*M. tuberculosis*]	♦ Pediatric hexavalent vaccine DTP-HepB-Polio-Hib (Shan6™) [*H. influenzae, B. pertussis*] [Indian regulatory authorities/May-21]

♦ Vaccine
DTP = Diphtheria, tetanus and pertussis
HepB = Hepatitis B
Hib = Haemophilus influenzae type B

*** Includes 2 projects not shown in the figure: 1 project in technical lifecycle and 1 project in Phase IV.

* See Appendix V for information about eligibility for R&D projects and Appendix VII for eligibility criteria of products.
** Listed on the 2019 WHO EML.

Phase II of clinical development targeting *S. pneumoniae* (Skypac), and an adaptive vaccine candidate targeting *H. influenzae* and *B. pertussis*: Shan6™.

A.2.4 No candidates targeting critical and/or urgent priorities

Sanofi does not have any candidates in its R&D pipeline targeting pathogens defined as 'critical' by WHO's list of priority pathogens and/or characterised as 'urgent' threats by the US Centers for Disease Control and Prevention (CDC).

A.3 Access plans for late-stage projects

Sanofi has four projects in late-stage development: two tuberculosis medicines and two vaccines.

Sanofi has ongoing clinical trials in access countries† for three out of its four late-stage projects. Sanofi plans to apply for WHO prequalification for both of its vaccine projects (paediatric DTP-HepB-Polio-Hib hexavalent vaccine Shan6™, and pneumococcal conjugate vaccine Skypac) to ensure access in GAVI-eligible countries. Sanofi does not report stewardship activities for its late-stage antituberculosis medicine projects.

B RESPONSIBLE MANUFACTURING Evaluated: antibacterials manufacturing (APIs and drug products)

B.1 Environmental risk-management for own sites and suppliers; tracks compliance with limits at own sites

Sanofi reports a strategy to minimise the environmental impact of wastewaters and solid waste from antibacterial manufacturing at its sites, including audits every three years. It reports setting discharge limits in the receiving environment for all antibacterials manufactured at its sites, based on PNECs to limit AMR, as recommended by the AMR Industry Alliance. Discharge levels are quantified at all sites using a mass balance approach, verified by chemical analysis if applicable. It reports that compliance of own sites with discharge limits is tracked.

Sanofi requires third-party suppliers of antibacterials APIs and drug products to follow similar standards, including limits based on PNECs. It reports conducting on-site audits every 1-5 years. It also requests and reviews the discharge levels of its suppliers. It reports 103 of 117 suppliers' sites, or 88% have been audited on various HSE topics including AMR. As part of such audits, suppliers are asked whether they have quantified discharge levels but it is unclear how many suppliers have done so.

There is limited information on the requirements it makes of external private waste-treatment plants. It does report auditing these plants which includes checking the suitability of technologies used for processing waste. It also reports employing conservative measures for effluents sent to external private and public wastewater plants.

B.2 Publicly discloses some information on environmental risk management and commitment to setting limits

Sanofi publishes some components of its environmental risk-management strategy. It is a member of the AMR Industry Alliance, which publishes a list of recommended antibacterial discharge targets. Sanofi publishes its commitment to setting these targets and assessing pharmaceutical levels in wastewaters. It publishes information on the progress towards its risk-management strategy for pharmaceuticals in the environment and HSE audits for priority suppliers (including antibacterial suppliers). Sanofi does not publish: (1) the results of environmental audits, conducted at its own sites, the sites of suppliers and/or external private and public waste-treatment plants; (2) a list of these suppliers and plants; or (3) the levels of antibacterial discharge from its own or suppliers' sites that manufacture antibacterials.

B.3 System in place to maintain production quality for own and suppliers' sites; no requests for official corrective action

Sanofi reports that its own sites and suppliers have a system to maintain high-quality antibacterial production consistent with international GMP standards. This includes periodic risk-based audits and tracking of corrective and preventive actions. Sanofi also requires its suppliers to audit their own suppliers. The Benchmark found no requests for official corrective action from the FDA or EMA related to non-conformities with cGMP at Sanofi's own sites or any subsidiaries that manufacture antibacterials.

C APPROPRIATE ACCESS & STEWARDSHIP – ACCESS

Evaluated: access activities relating to antibacterial & antifungal medicines & vaccines in 102 access countries†

Sanofi is not eligible for indicators: C.1.1 and C.2.1. For more information, see Appendix VII.

C.1.2 Filed to register off-patent/generic medicines in 13 access countries on average

Sanofi performs above average, filing all its 10 off-patent/generic medicines for registration in access countries. Its most widely filed relevant product is the antifungal metronidazole, filed in 48 access countries. Five of its relevant products are filed in less than ten access countries. Four of its relevant products are filed for registration in at least one LIC.

C.1.3 Filed to register on-patent vaccines in 40 access countries on average

Sanofi performs above average, filing all its three relevant on-patent vaccines for registration in access countries. Its most widely filed relevant vaccine is Hexaxim®, filed in 54 access countries. Hexaxim® is followed by the meningococcal conjugate vaccine Menactra®, filed in 48 countries. Sanofi filed all its three relevant on-patent vaccines for registration in at least one LIC.

C.2.2 Several strategies to expand access to off-patent/generic medicines

Sanofi performs above average, with access strategies reported for five of its 10 relevant off-patent/generic medicines. It expands access to its off-patent/generic medicines in access countries through a voluntary licensing agreement, donations and tenders. In 2020, Sanofi coordinated the donation of 9,300 packs of metronidazole for emergency kits preparation and 55,000 packs of amoxicillin in Colombia. In 2020, it supplied more than 9 mn packs of isoniazid and more than 1.2 mn packs of rifampicin containing regimens through a government tender for tuberculosis in South Africa, with prices up to 45% lower than those offered in the private sector.

C.2.3 Several strategies to expand access to on-patent vaccines

Sanofi performs above average, with access strategies reported for all its three relevant on-patent vaccines. It expands access in access countries through equitable pricing, tenders and public or private partnerships. Sanofi has a tiered pricing policy where price is defined by the channel of distribution and countries' GNI per capita. It partners with UNICEF to provide Shan5™ at a defined price. Sanofi provides evidence of patient reach and geographic reach for some of its reported approaches. In 2020, it estimates to have reached more than 5 mn people worldwide with Hexaxim®.

† 102 low- and middle-income countries where better access to medicine is most needed.

C.3 Several strategies to ensure continuous supply

Sanofi performs above average, with strategies reported in all four areas assessed. Sanofi ensures accurate demand planning and data sharing by having a monthly process for supply planning with a 36-month time horizon. Sanofi has a "zero out-of-stock" objective with short-term (up to 36 months) and long-term (36 months to 5-10 years) forecasts. Sanofi mitigates against shortage risks by keeping buffer stocks. It produces some of its APIs in-house and ensures dual sourcing for all other APIs.

Sanofi reports four capacity building or technology transfer initiatives, in India, Nigeria and Vietnam. To mitigate against substandard and falsified products, Sanofi has an anti-counterfeiting coordination network, a security department to detect online illicit sales and a central laboratory of counterfeit analysis.

C APPROPRIATE ACCESS & STEWARDSHIP – STEWARDSHIP

Evaluated: stewardship activities relating to antibacterial & antifungal medicines globally

C.4 Comprehensive COI mitigation strategies in place for its educational programme

Sanofi performs strongly in conflict of interest (COI) mitigation for the one AMR-related educational programme for HCPs assessed by the Benchmark. The programme has all three COI mitigation strategies looked for by the Benchmark: (1) content is developed independently from its marketing department; (2) participants are not provided financial or material incentives (as it is a website); and (3) a policy of not using branded materials.

C.5 Engages in sales and marketing practices to address appropriate use

Sanofi performs above average in sales practices. It does not deploy any sales agents to promote its antibacterial and/or antifungal medicines to healthcare professionals outside of France. However, for its sales in France, which are only for pristinamycin (Pyostacine®), Sanofi reports that it partly decouples incentives for sales agents from sales volumes of this product.

Sanofi engages in marketing practices that aim to address the appropriate use of its antibacterial and/or antifungal medicines. Its marketing materials reflect emerging resistance trends and/or include treatment guidelines for healthcare professionals: for pristinamycin (Pyostacine®).

C.6 Does not report adapting brochures and/or packaging to facilitate appropriate use by patients

Sanofi does not report adapting brochures and/or packaging to facilitate the appropriate use of its antibacterial and/or antifungal medicines by patients.

C.7 Active in one AMR surveillance programme; openly publishes aggregated results

Sanofi funds a national programme managed by the National Reference Centre for Pneumococci (NRCP) with the French Regional Pneumococcal Observatories. It is focused on *S. pneumoniae* in France and has been running since 2000. Only the aggregated results are shared by NRCP through peer-reviewed open-access journal articles.

Overall Performance

2020 2021

63% 58%▼

Shionogi & Co, Ltd

Large R&D-based pharmaceutical company

Stock exchange: TSE • Ticker: 4507 • HQ: Osaka, Japan • Employees: 5,233

PERFORMANCE

Shionogi performs average overall in its evaluated Research Areas compared to the other large research-based pharmaceutical companies in scope.

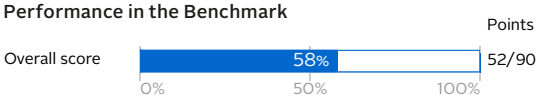
R&D: Shionogi performs well in R&D. Eight of its 11 projects target critical and/or urgent pathogens. For the first time Shionogi has a vaccine in their pipeline. Shionogi is working on improving access and stewardship of its antibacterial cefiderocol.

Responsible Manufacturing: Shionogi leads. Reports comprehensive environmental risk-management strategy for own sites and suppliers; co-leads in compliance with limits at own sites; leads in public disclosure of strategy and compliance

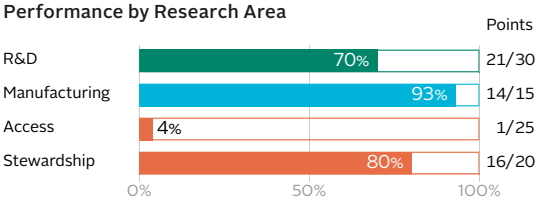
Appropriate Access: Performs low. Its relevant on- and off-patent products are not available in access countries.

Stewardship: Performs well. It fully decouples incentives for sales agents from sales volumes. It publicly shares aggregated results of its surveillance programmes. It reports comprehensive conflict of interest mitigation for its educational programmes. It adapts brochures for patients.

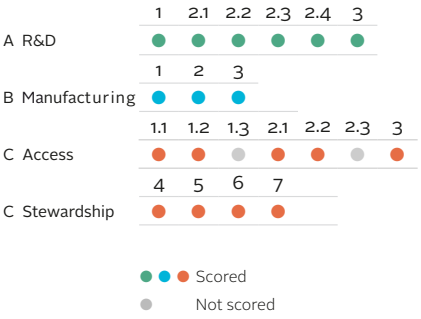
Performance in the Benchmark



Performance by Research Area



How Shionogi was evaluated



OPPORTUNITIES FOR SHIONOGI

Expand breadth of R&D pipeline and depth of R&D access and stewardship plans. Shionogi has one of the most diverse pipelines across all large research-based companies in the AMR Benchmark. It can expand the focus of its pipeline to target resistant pathogens for which R&D is limited, such as *Campylobacter* spp. and *H. pylori*. For its recently approved cefiderocol (Fetroja®/ Fetcroja®), Shionogi engages with generic medicines manufacturers and access-related organisations such as GARDP and the Clinton Health Access Initiative to increase affordability and availability. Shionogi can intensify these engagements to reach more patients and countries. Shionogi can continue to build towards a comprehensive surveillance programme to ensure cefiderocol is not used excessively.

Expand registration to cefiderocol (Fetroja®/ Fetcroja®) in access countries. Shionogi can file cefiderocol (Fetroja®/ Fetcroja®) for registration in access countries. Further, to accelerate the availability of cefiderocol in access countries Shionogi can consider voluntary non-exclusive licensing, compassionate use programmes and public/private partnerships.

Expand adaptations to brochures and packaging to consider more patient needs. Shionogi adapts brochures to take account of paediatric use to support the appropriate use of cefcapene pivoxil (Flomox®) by patients. It can further adapt its brochures and packaging of all antibacterial and antifungal medicines to consider local languages, literacy levels, environmental conditions and patient adherence to treatment.

Publicly share raw data from surveillance programmes. Shionogi runs the multinational SIDERO-WT programme, which is focused on resistance against antibacterials targeting Gram-negative bacteria. It can publicly share raw data from this surveillance programme, following through on commitments to share this with the AMR Register in 2021. Additionally, either Shionogi or the managing partners should publicly share raw data from the other surveillance programmes it is involved in.

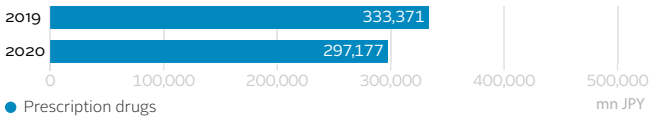
CHANGES SINCE 2020

- In response to an opportunity from the 2020 AMR Benchmark, in July 2021, Shionogi entered into a collaboration with the Global Antibiotic Research and Development Partnership (GARDP) and the Clinton Health Access Initiative (CHAI) to accelerate access, including in LMICs, to the antibiotic cefiderocol.
- In October 2020, Shionogi expanded investments into vaccine development through a licensing partnership agreement with HanaVax for research, development, manufacturing, distribution and commercialisation of their *S. pneumoniae* nasal vaccine candidate.
- In its 2020 Environmental Report, Shionogi discloses compliance with limits of its own and suppliers' sites, some details of audit results and some names and/or locations of its suppliers and sole waste contractor.
- In 2020, Shionogi started to support the SENTRY programme for the surveillance of cefiderocol. The results are shared publicly via open-access journal articles and the SENTRY website.

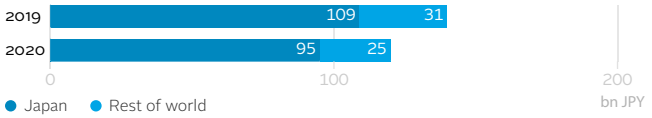
SALES AND OPERATIONS

Therapeutic areas: Infectious diseases, Psycho-neurological diseases
Business segments: Prescription drugs
Product categories: Generic medicines, Innovative medicines, Vaccines
M&A since 2020: In July 2020, Shionogi entered into agreement with Ping An Life Insurance of China, Ltd. to establish of a joint venture called Ping An Shionogi Company Ltd

Revenue by business segment



Revenue by region



PIPELINE *for pathogens in scope*

Pipeline size: 11 projects targeting pathogens in scope* (8 antibacterial medicines; 1 antibacterial vaccine; 2 antifungal medicines).
Development stages: 5 discovery programmes for antifungals, antituberculosis and antibacterial candidates; 2 preclinical projects including an antibody against *P. aeruginosa* and a vaccine for *S. pneumoniae*; and 1 Phase II adaptive project.
Novelty: 0 novel clinical-stage medicine projects.
'Critical' and/or 'urgent' pathogens: 8 projects, cefiderocol (Fetroja®/Fetcroja®) and its adaptations target CRAB, CRE and CRPA. Furthermore, Shionogi has discovery/preclinical projects targeting *C. auris* and *P. aeruginosa*.
Regulatory approvals: 3 approvals. In November 2019, cefiderocol (Fetroja®/Fetcroja®) was approved by the FDA for the treatment of complicated urinary tract infections (cUTIs), including pyelonephritis. In September 2020, the FDA approved the supplemental indication for the treatment of hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP). In April 2020 the EMA approved cefiderocol (Fetroja®/Fetcroja®) for the treatment of gram-negative bacterial infections.

PORTFOLIO *for pathogens in scope*

Comparatively small portfolio: At least 8 products: 8 antibacterial medicines
On-patent medicine: 1 (cefiderocol)
Off-patent/generic medicines: 7 of which 2 were selected for analysis* (cefcapene [W], flomoxef [W])
AWaRe medicines:** 2 Access group; 5 Watch group

Pipeline for priority pathogens

Products on the market

PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT Evaluated: medicine & vaccine pipelines for priority* bacteria & fungi

A.1 Highest relative investment in R&D
Shionogi discloses to the Benchmark its R&D investments during 2019 and 2020 in antibacterial and antifungal medicines and/or vaccines for pathogens in scope. Shionogi reports that it invested USD 74.22 mn in R&D for antibacterial and antifungal medicines and vaccines in 2019 and 2020. Shionogi invests the highest proportion of its revenues in R&D in this area and the third highest absolute amount compared to the other companies who reported investments to the Benchmark.. Shionogi has pledged USD 20 mn to the AMR Action Fund over the next ten years.

Pipeline targeting priority pathogens: 11 *As at 24 September 2021*

Discovery	Pre-clinical	Phase I	Phase II	Phase III	Approval
Antituberculosis programme 1	Antibody [*P. aeruginosa*]		Fetroja®/Fetcroja® - additional population: paediatric		Cefiderocol (Fetroja®/Fetcroja®) [FDA; Nov-19] cUTI [*Enterobacteriaceae*] [EMA; Apr-20] Gram-negative bacterial infections [FDA; Sep-20] HABP/VABP [*Enterobacteriaceae*]
Antituberculosis programme 2	♦ *S. pneumoniae* vaccine				
Antifungal programme 1					
Antifungal programme 2					
Antibacterial programme 3					

♦ Vaccine
cUTI = Complicated urinary tract infection
HABP = Hospital-acquired bacterial pneumonia
VABP = Ventilator-associated bacterial pneumonia

* See Appendix V for information about eligibility for R&D projects and Appendix VII for eligibility criteria of products.
** Listed on the 2019 WHO EML.

A.2.1 Medium-sized diverse pipeline
The company reports 11 projects targeting pathogens in scope: ten medicines and one vaccine, nine targeting bacterial pathogens and two targeting fungal pathogens. Out of the 11 projects, five are in discovery stage, two are in preclinical development, one is in clinical development and three received marketing approval during the period of analysis.

A.2.2 No clinical-stage novel projects
Shionogi's clinical-stage medicine pipeline consists of one innovative R&D medicine, cefiderocol, a siderophore cephalosporin antibacterial for the treatment of multi-drug resistant infections. Cefiderocol (Fetroja®/ Fetcroja®) obtained marketing approval for the treatment of complicated urinary tract infections (cUTIs), including pyelonephritis, from the FDA in November 2019, and for HABP/VABP in September 2020. In April 2020, it received approval from the EMA for the indication of gram-negative bacterial infections. Cefiderocol is in Phase II trials for the extension of its indication to treat children. Cefiderocol does not meet any of WHO's innovativeness criteria.

A.2.3 Newly active in vaccine development
Shionogi reports one innovative vaccine project in its pipeline. It consists of a preclinical vaccine candidate against *S. pneumoniae* developed in collaboration with HanaVax Inc.

A.2.4 Investing in early stage programmes targeting critical and/or urgent priorities
Shionogi has eight projects targeting pathogens defined as 'critical' by WHO's list of priority pathogens and/or characterised as 'urgent' threats by the US Centers for Disease Control and Prevention (CDC). Cefiderocol, which accounts for four of these projects, targets several MDR gram-negative pathogens such as *A. baumanii* and Carbapenem-resistant/ESBL-resistant *Enterobacteriaceae*. Shionogi is carrying out several discovery and preclinical programmes targeting *P. aeruginosa* and *C. auris*.

A.3 Plans to improve access and stewardship for cefiderocol
Shionogi has four projects in its late-stage pipeline, all related to different indications of the same compound, cefiderocol, first marketed in December 2019.
Shionogi reports having an ongoing Global Compassionate Use programme for cefiderocol. It is discussing a potential technology transfer agreement with generic medicine manufacturers to extend access to cefiderocol to other territories. It is also building partnerships with not-for-profit organisations to build a system to support stewardship of cefiderocol. Shionogi reports plans to conduct surveillance of cefiderocol. Shionogi applied for the inclusion of cefiderocol in the WHO's EML and suggested including it in the Reserve (AWARE) category.

B RESPONSIBLE MANUFACTURING Evaluated: antibacterials manufacturing (APIs and drug products)

B.1 Comprehensive environmental risk-management for own sites and suppliers; tracks compliance with limits at own sites and suppliers
Shionogi reports a comprehensive strategy to minimise the environmental impact of wastewaters and solid waste from antibacterial manufacturing at its sites, including audits every five years. It reports setting discharge limits in the receiving environment for all antibacterials manufactured at its site, based on PNECs to limit AMR, as recommended by the AMR Industry Alliance, or the EMA. It also reports quantifying discharge levels at its site using a mass balance approach, verified by chemical analysis if applicable. Its sole manufacturing site in scope is reported to be fully compliant with discharge limits.

Shionogi requires third-party suppliers of antibacterials to follow the same standards, including limits based on PNECs. It reports conducting on-site audits every five years. It requests and reviews the discharge levels of its suppliers. It also reports five out of nine supplier sites have quantified discharge levels and three, or 33%, of those are compliant with discharge limits.

Shionogi expects its only external private waste-treatment plant to comply with its general environmental standards. It audits this plant every year which includes the suitability of technologies used for processing waste and protocols for preventing contamination. All solid waste and wastewater sent to this plant is set to be incinerated.

B.2 Publicly discloses information on environmental risk management; aggregated audit results and compliance with limits
Shionogi leads in public disclosure of its environmental risk-management strategy. It publishes some information on audit results, based on its ERM strategy, and covers wastewater management, solid waste management and discharge limits. It is a member of the AMR Industry Alliance, which publishes a list of recommended antibacterial discharge targets. It publicly discloses that all 5 antibacterials manufactured at its own site are compliant with discharge limits. In addition, it is publicly disclosed that five out of nine supplier sites have quantified discharge levels and three, or 33%, of those, which supply flomoxef (Flumarin®), doripenem (Doribax®) and sulfamethoxazole/trimethoprim (Bakuta®), are compliant with discharge limits. It also publishes a table listing its antibacterials in scope, their connection to own sites and suppliers, and which are compliant with discharge limits. Further, it publishes where five of its suppliers in scope are located (Japan and India) and the respective products supplied by each. The name of its only external private waste-treatment plant in scope is also disclosed.

B.3 System in place to maintain production quality for own and suppliers' sites; no requests for official corrective action
Shionogi reports that its own sites and suppliers have a system to maintain high-quality antibacterial production consistent with international GMP standards. This includes periodic risk-based audits and tracking of corrective and preventive actions. Shionogi also requires its suppliers to audit their own suppliers. The Benchmark found no requests for official corrective action from the FDA or EMA related to non-conformities with cGMP at Shionogi's own sites or any subsidiaries that manufacture antibacterials.

C APPROPRIATE ACCESS & STEWARDSHIP – ACCESS
Evaluated: access activities relating to antibacterial & antifungal medicines & vaccines in 102 access countries***

Shionogi is not eligible for indicators: C.1.3 and C.2.3. For more information, see Appendix VII.

C.1.1 No filings for relevant on-patent medicines
Shionogi's performance is low as it has not yet filed its relevant on-patent medicine in access countries. Its relevant on-patent medicine is the antibiotic cefiderocol (Fetroja®/Fetcroja®), used to treat infections caused by aerobic Gram-negative bacteria when there are few treatment options available. It was approved by the FDA in 2019 . Cefiderocol is newly included in the WHO 22nd EML (2021) as a 'Reserve' group antibiotic effective against multi-drug resistant bacteria.

C.1.2 Limited filings for relevant off-patent medicines
Shionogi's performance is low. It filed its off-patent antibiotics flomoxef and cefcapene, used to treat several bacterial infections, in one access country (China).

*** 102 low- and middle-income countries where better access to medicine is most needed.

C.2.1 No access strategy for relevant on-patent medicine

Shionogi's performance is low as it does not report strategies to expand access to its relevant on-patent medicine in access countries during the period of analysis. However, in July 2021, Shionogi, GARDP and CHAI announced a MOU to accelerate access to cefiderocol in low- and middle-income countries.

C.2.2 Expanding access to off-patent/generic medicines

Shionogi's performance is low as it does not provide access to its two relevant off-patent/generic antibacterial medicines, flomoxef and cefcapene, in access countries. These two medicines did not meet all regulatory requirements because their respective clinical trials were conducted prior to the ICH guidelines. Shionogi does not actively promote these medicines. However, in July 2021, GARDP identified flomoxef as a potential treatment option for neonatal sepsis.

C.3 No supply in access countries

Shionogi's performance is low as it does not yet make its relevant products available in access countries.

C APPROPRIATE ACCESS & STEWARDSHIP – STEWARDSHIP

Evaluated: stewardship activities relating to antibacterial & antifungal medicines globally

C.4 Comprehensive COI mitigation strategies in place for its educational programmes

Shionogi performs strongly in conflict of interest (COI) mitigation for the five AMR-related educational programmes for HCPs assessed by the Benchmark. To mitigate COI for one programme, it provides financial resources to an independent third party (Radio Nikkei) to develop the programme. The remaining four programmes have all three COI mitigation strategies looked for by the Benchmark: (1) content is developed independently from its marketing department; (2) a pledge not to provide financial or material incentives to participants; and (3) it does not use branded materials.

C.5 Fully decouples incentives for sales agents from sales volumes, and engages in marketing practices to address appropriate use

Shionogi performs strongly in sales practices. It reports that it fully decouples incentives for sales agents from sales volumes of its antibacterial and/or antifungal medicines.

Shionogi engages in marketing practices that aim to address the appropriate use of its antibacterial and/or antifungal medicines. Its marketing materials reflect emerging resistance trends and/or include treatment guidelines for healthcare professionals: for cefiderocol (Fetroja®/Fetcroja®), doripenem (Finibax®) and flomoxef (Flumarin®).

C.6 Makes one type of brochure and/or packaging adaptation to facilitate appropriate use by patients

Shionogi adapts brochures to facilitate the appropriate use of cefcapene pivoxil (Flomox®) by patients. Shionogi is middle-performing in this measure, taking account of paediatric use. It has created a brochure that is easy to understand using simple illustrations, which is tailored to the treatment of children to improve paediatric use.

C.7 Active in multiple AMR surveillance programmes; openly publishes aggregated results

Shionogi is active in multiple AMR surveillance programmes. It runs the multinational SIDERO-WT programme, which is focused on resistance against Gram-negative bacteria in 13 countries and has been running since 2014. Shionogi only shares the aggregated results through peer-reviewed open-access journal articles, however, within 2021, it is planning to share the raw data on the AMR Register, an open-access data platform. For the remaining programmes, the aggregated results are shared through peer-reviewed open-access journal articles, as well as on an open-access data platform for the SENTRY programme (a programme managed by JMI laboratories).

Overall Performance

2020 2021

53% 69%▲

Abbott Laboratories

Generic medicine manufacturer

Stock exchange: NYSE • Ticker: ABT • HQ: Chicago, IL, US • Employees: 109,000

PERFORMANCE

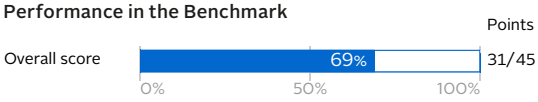
Abbott performs well overall in its evaluated Research Areas compared to the other generic medicine manufacturers in scope.

Responsible Manufacturing: Performs well. Reports comprehensive environmental risk-management strategy for own sites and suppliers; quantifies discharge levels at all own sites.

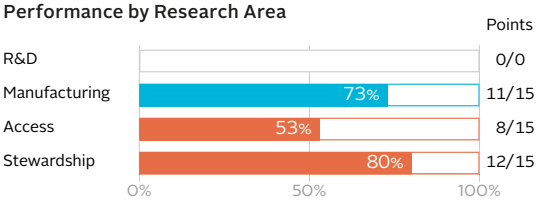
Appropriate Access: Middle-performing. Files some of its off-patent/ generic medicines for registration in access countries. Reports some strategies to expand access and ensure continuous supply of its relevant product.

Stewardship: Performs well. It ran a pilot where it fully decoupled incentives for sales agents from sales volumes for an anti-infective, however it does not decouple such incentives for its other products. It reports broad conflict of interest mitigation for its educational programmes. It adapts packaging for patients.

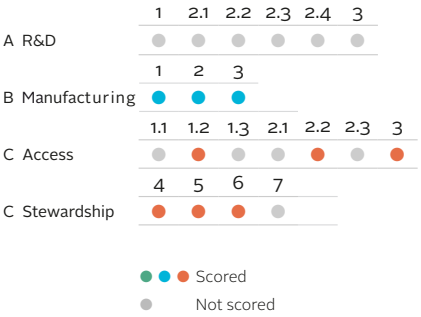
Performance in the Benchmark



Performance by Research Area



How Abbott was evaluated



OPPORTUNITIES FOR ABBOTT

Request and review discharge levels of all suppliers and increase public disclosure on environmental risk management. Abbott can expand its environmental risk management requirements to all suppliers by fully implementing its supplier contract templete which outlines specific provisions for AMR. Abbott currently requests and reviews discharge levels for only a subset of its suppliers. Abbott can also publicly disclose more information on how it manages environmental risk related to antibacterial manufacturing. It can publish information on its progress in implementing the strategy, the limits it sets, and the results of the audits of own and suppliers' sites including antibacterial discharge levels.

Expand registration and ensure availability of antibacterial and antifungal medicines. Abbott can expand registration of its antibiotics and antifungals listed on the 2021 WHO EML, such as gentamicin, itraconazole and tigecycline, to more countries, including low-income countries, with a high burden of disease. Further, it can expand equitable access in countries where medicines have been registered.

Fully decouple incentives for sales agents from sales volumes. Abbott ran a pilot in India where it fully decoupled incentives for sales agents from sales volumes of an anti-infective for three months. It can expand this practice to more countries where it markets antibacterial and/or antifungal medicines and to more relevant products.

Comprehensively mitigate COI for educational programmes. Abbott organises medical education programmes for healthcare professionals on responsible use of antimicrobial medicines. It can ensure that branded materials are not used in any educational programmes, as is now the case for some.

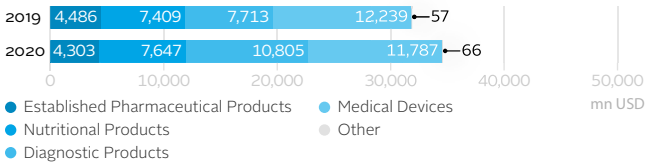
CHANGES SINCE 2020

- In 2021, Abbott introduced a new contract template for suppliers of APIs and drug products with clauses that specifically require implementation of AMR standards.
- In response to an opportunity from the 2020 AMR Benchmark, Abbott ran a new pilot in which it fully decoupled incentives for sales agents from sales volumes of an anti-infective in India for three months.
- Abbott is funder and member of the consortium VALUE-Dx. VALUE-Dx is the first Innovative Medicines Initiative project initiated by six *in vitro* diagnostic companies who work with 20 non-industry partners to combat AMR and improve patient outcomes.
- Since 2020, Abbott has adapted packaging of eight of its antibacterial medicines, including amoxicillin and azithromycin, to take account of adherence to treatment, literacy and paediatric use to facilitate the appropriate use of such medicines by patients.

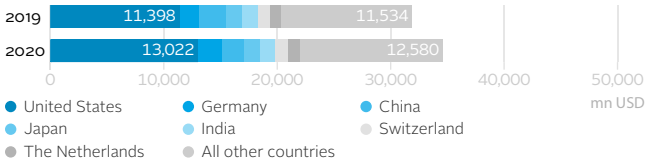
SALES AND OPERATIONS

Therapeutic areas: Cardiovascular, Diabetes care, Gastro intestinal/immunity health, Infectious disease (Diagnostic, Covid-19), Metabolic disorders, Pain/central nervous system, Respiratory, Women's health.
Business segments: Established pharmaceutical products, Nutritional products, Diagnostic products, Medical devices
Product categories: Diagnostics, Generic medicines, Medical devices, Vaccines
M&A since 2020: None in the antibacterial and/or antifungal sectors

Net sales by business segment



Net sales by region



PORTFOLIO *for pathogens in scope*

Comparatively large portfolio: At least 85 products: 75 antibacterial medicines; 3 antibacterial vaccines; 7 antifungal medicines
Off-patent/generic medicines: 10 of 85 were selected for analysis* (amoxicillin/clavulanic acid [A], amphotericin b [F], cefixime [W], clarithromycin [W], clofazimine [T], colistin [R], gentamicin [A], itraconazole [F], linezolid [T], tigecycline [R])
AWaRe medicines:** 16 Access group; 20 Watch group; 3 Reserve group
Anti-TB medicines: 10

Products on the market

PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT

As a generic medicine manufacturer, Abbott is not evaluated in this Research Area.

B RESPONSIBLE MANUFACTURING Evaluated: antibacterials manufacturing (APIs and drug products)

B.1 Comprehensive environmental risk-management for own sites and suppliers; tracks compliance with limits at own sites

Abbott reports a comprehensive strategy to minimise the environmental impact of wastewaters and solid waste from antibacterial manufacturing at its sites, including audits every three years. It reports setting discharge limits in the receiving environment for all antibacterials manufactured at its sites, based on PNECs to limit AMR, as recommended the AMR Industry Alliance. Discharge levels are quantified using a mass balance approach, verified by chemical analysis if applicable. It reports tracking compliance with discharge limits of own sites.

Abbott requires third-party suppliers of antibacterials to follow the same standards, including limits based on PNECs. It reports conducting on-site audits every 3-5 years. It requests and reviews the discharge levels of its suppliers. A subset of its suppliers' sites report to have quantified discharge levels.

Abbott expects external private waste-treatment plants to comply with its general environmental standards. It audits these plants at least every five years (based on risk) which includes checking the suitability of technologies used for processing waste and protocols for preventing contamination. It also employs conservative measures for effluents sent to external private and public wastewater treatment plants.

B.2 Limited publicly available information on environmental risk management

Abbott publishes some components of its environmental risk-management strategy, without specific references to AMR. It does publish having a programme in place to assess and minimise the impact of discharges, from own and suppliers' sites manufacturing APIs, on the environment. Abbott does not publish: (1) the results of environmental audits, conducted at its own sites, the sites of suppliers and/or external private and public waste-treatment plants; (2) a list of these suppliers and plants; or (3) the limits and levels of antibacterial discharge from its own or suppliers' sites.

B.3 System in place to maintain production quality for own and suppliers' sites; no requests for official corrective action

Abbott reports own sites and suppliers have a system to maintain high-quality antibacterial production consistent with international GMP standards. This includes periodic risk-based audits and tracking of corrective and preventive actions. Abbott also requires its suppliers to audit their own suppliers. The Benchmark found no requests for official corrective action from the FDA or EMA related to non-conformities with cGMP at Abbott's own sites or any subsidiaries that manufacture antibacterials.

* See Appendix VII for information about eligibility criteria for products.
** Listed on the 2019 WHO EML.

C APPROPRIATE ACCESS & STEWARDSHIP – ACCESS

Evaluated: access activities relating to antibacterial & antifungal medicines & vaccines in 102 access countries***

Abbott is not eligible for indicators: C1.1, C1.3, C.2.1 and C.2.3. For more information, see Appendix VII.

C.1.2 Filed to register 8 of 10 relevant off-patent/generic medicines in 8 access countries on average

Abbott has an average performance, filing eight of its ten relevant off-patent/generic medicines for registration in eight access countries on average. Its most widely filed relevant product is the antibiotic clarithromycin filed in 58 access countries. Seven of its relevant products are filed in less than ten access countries. One of its relevant products is filed for registration in at least one LIC.

C.2.2 Limited information on strategies to expand access to off-patent/generic medicines

Abbott has an average performance as it reports limited information on how it expands access to its ten relevant off-patent/generic medicines.

Abbott reports two simplified treatment regimens examples in Bolivia, India, and Peru. It estimates its simplified treatment regimen containing clarithromycin to reach 5,000 cumulative patients per year in Peru and Bolivia.

C.3 Several strategies to ensure continuous supply

Abbott has an average performance, with strategies reported in all four areas assessed. It ensures accurate demand planning and data sharing by having a monthly rolling forecast with a 24-months horizon. Abbott mitigates against shortage risks by keeping a buffer stock for critical APIs and finished products. It has a dual-sourcing strategy for its strategic APIs. Abbott reports one technology transfer initiative of its drug product unit operations to a third-party drug manufacturer. To mitigate against substandard and falsified products, Abbott uses packaging features, conducts employee's trainings, and tests potential falsified products in a dedicated laboratory.

C APPROPRIATE ACCESS & STEWARDSHIP – STEWARDSHIP

Evaluated: stewardship activities relating to antibacterial & antifungal medicines globally

C.4 Broad COI mitigation strategies in place for its educational programmes

Abbott performs well in conflict of interest (COI) mitigation for the five AMR-related educational programmes for HCPs assessed by the Benchmark. To mitigate COI for three programmes, it provides financial resources to independent third parties (APUA, Medscape, BSAC and the University of Dundee) to develop the programme. One programme has all three COI mitigation strategies looked for by the Benchmark: (1) content is developed independently from its marketing department; (2) a pledge not to provide financial or material incentives to participants; and (3) it does not use branded materials. The remaining programme has two of three COI mitigation strategies looked for by the Benchmark: it is unclear whether branded materials are being used.

C.5 Engages in sales and marketing practices to address appropriate use

Abbott performs above average in sales practices. It ran a pilot in 2021 where it fully decoupled incentives for sales agents from sales volumes of an anti-infective in India for three months. However, outside of this pilot Abbott does not report whether it decouples incentives for sales agents from sales volumes to help prevent the inappropriate use of its antibacterial and/or antifungal medicines.

Abbott engages in marketing practices that aim to address the appropriate use of its antibacterial and/or antifungal medicines. Its marketing materials reflect emerging resistance trends and/or include treatment guidelines for healthcare professionals: for clarithromycin.

C.6 Makes three types of brochure and/or packaging adaptations to facilitate appropriate use by patients

Abbott adapts packaging to facilitate the appropriate use of its antibacterial medicines by patients. Abbott performs strongly in this measure, taking account of adherence to treatment, literacy and paediatric use. It adapts the package size of clarithromycin in eight countries to a full treatment course of either a 7-, 10-, or 14-day treatment. Moreover, Abbott has dose marking on the packaging of cefixime in India to improve patient adherence to treatment. Further, it includes a QR code on the packaging of amoxicillin that directs patients to information on the appropriate use and the course of treatment to improve adherence to treatment. Additionally, Abbott adapts packaging for antibacterial medicines in India by including pictograms to support literacy challenges. Finally, it includes a QR code on the packaging of eight antibacterial paediatric suspensions that directs to a video explaining how to use them appropriately.

C.7 AMR Surveillance

As a generic medicine manufacturer, Abbott is not assessed in this indicator but its activities in AMR surveillance are reported. The Benchmark notes that Abbott is active in two AMR surveillance programmes. It runs the national ARISE programme, which is focused on regional sensitivity indices at a state level on hospital- and community-acquired infections in India since January 2019. Abbott only shares the data collected in this programme through a data platform in a restricted manner. Moreover, the CANWARD programme is a national programme managed by the Canadian Antimicrobial Resistance Alliance with support from Abbott, among others. Only the aggregated results are shared through an open-access data platform, as well as through peer-reviewed journal articles.

*** 102 low- and middle-income countries where better access to medicine is most needed.

Overall Performance

2020 2021

14% 20%▲

Alkem Laboratories Ltd

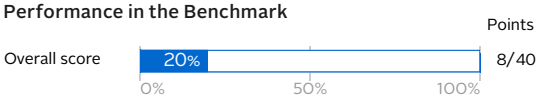
Generic medicine manufacturer

Stock exchange: NSE • Ticker: ALKEM • HQ: Mumbai, India • Employees: 14,331

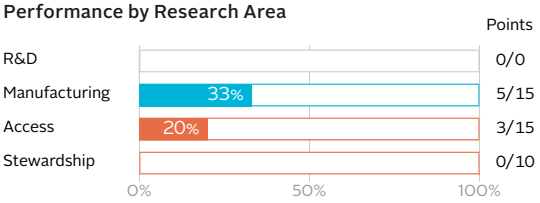
PERFORMANCE

Alkem performs low overall in its evaluated Research Areas when compared to the other generic medicine manufacturers in scope.
Responsible Manufacturing: Performs low. Reports a general environmental risk-management strategy but without a specific aim to limit AMR.
Appropriate Access: Performs low. Discloses no information on registration filings, expanding access or ensuring continuous supply for its off-patent/generic medicines.
Stewardship: Performs low. It does not report decoupling incentives for sales agents from sales volumes. It does not adapt brochures or packaging for patients.

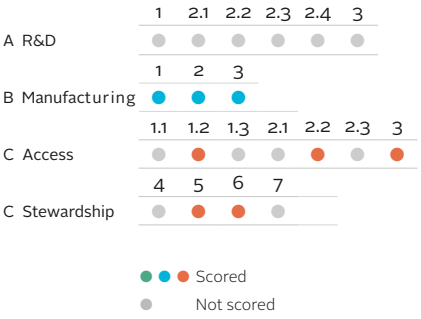
Performance in the Benchmark



Performance by Research Area



How Alkem was evaluated



OPPORTUNITIES FOR ALKEM

Develop an AMR-specific environmental risk-management strategy and increase public disclosure. Alkem reports a commitment to manufacture its products in an environmentally responsible manner without specifying whether AMR is taken into account. The company can develop an AMR strategy for its own manufacturing sites, the sites of suppliers and external private waste-treatment plants, based on the guidelines of the AMR Industry Alliance. This includes setting limits and quantifying discharge levels to track compliance. Moreover, Alkem can publish information on how it manages environmental risk related to antibacterial manufacturing to curb AMR. The company currently publishes limited information.
Expand registration and ensure availability of antibacterial and antifungal medicines. Alkem can expand registration and ensure equitable access of its antibiotics and antifungals listed on the 2021 WHO EML, such as cefotaxime and tigecycline, to more countries, including low-income countries, with a high burden of disease. It can improve transparency on where its medicines are registered and made available.
Apply responsible sales practices for antibacterial and antifungal medicines. Alkem can apply responsible sales practices for antibacterial and antifungal medicines by not deploying sales agents. Alternatively, it can fully decouple incentives for sales agents from sales volumes of such medicines.

CHANGES SINCE 2020

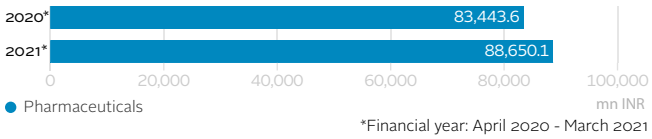
No changes are reported for Alkem.

* All companies were assessed based on data submitted to the Benchmark in the current and previous periods of analysis, as well as information the companies have made publicly available, or that are accessible through other sources. For the 2021 Benchmark, Alkem declined to submit data to the Antimicrobial Resistance Benchmark.

SALES AND OPERATIONS

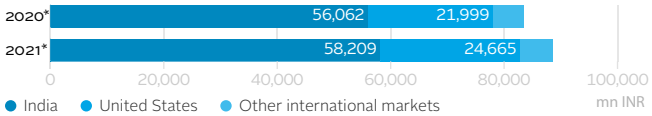
Therapeutic areas: Anti-diabetes, Anti-infective, Cardiac, Dermatology, Gastro-intestinal, Pain/analgesics, Neuro/CNS.
Business segments: Pharmaceuticals
Product categories: Generic medicines
M&A since 2020: None in the antibacterial and/or antifungal sectors

Total income by business segment



*Financial year: April 2020 - March 2021

Total income by region



*Financial year: April 2020 - March 2021

PORTFOLIO *for pathogens in scope*

Mid-sized portfolio: At least 52 products: 49 antibacterial medicines; 3 antifungal medicines
Off-patent/generic medicines: 10 of 52 were selected for analysis** (amoxicillin [A], amoxicillin/clavulanic acid [A], caspofungin [F], cefixime [W], cefotaxime [W], colistin [R], isoniazid [T], itraconazole [F], linezolid [T], tigecycline [R])
AWaRe medicines***: 5 Access group; 18 Watch group; 3 Reserve group
Anti-TB medicines***: 2

Products on the market

PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT

As a generic medicine manufacturer, Alkem is not evaluated in this Research Area.

B RESPONSIBLE MANUFACTURING Evaluated: antibacterials manufacturing (APIs and drug products)

B.1 No AMR-specific environmental risk management strategy

Alkem states a general commitment to manufacture its products in an environmentally responsible manner, supported by a management system that includes periodic impact assessments. It is unclear how the strategy takes AMR into account or aims to minimise the environmental impact of wastewaters and solid waste from antibacterial manufacturing at its own sites, third-party suppliers of antibacterials or external private and public waste-treatment plants.

B.2 Limited publicly available information on environmental risk management

Alkem publishes limited information on its approach to environmental risk-management, without specific references to AMR. It does not publish: (1) the results of environmental audits, whether conducted at its own sites, the sites of suppliers or external private and public waste-treatment plants; (2) a list of these suppliers and plants; or (3) the limits and levels of antibacterial discharge from its own or suppliers' sites.

B.3 System in place to maintain production quality for own and suppliers' sites; no requests for official corrective action

Alkem reports that its own sites and suppliers have a system to maintain high-quality antibacterial production consistent with international GMP standards. This includes periodic risk-based audits and tracking of corrective and preventive actions. There is limited information on whether Alkem requires its suppliers to audit their own suppliers. The Benchmark found no requests for official corrective action from the FDA or EMA related to non-conformities with cGMP at Alkem's own sites or any subsidiaries that manufacture antibacterials.

** See Appendix VII for information about eligibility criteria for products.
*** Listed on the 2019 WHO EML.

C APPROPRIATE ACCESS & STEWARDSHIP – ACCESS

Evaluated: access activities relating to antibacterial & antifungal medicines & vaccines in 102 access countries†

Alkem is not eligible for indicators: C.1.1, C.1.3, C.2.1 and C.2.3 For more information, see Appendix VII.

C.1.2 No information on registration filings for off-patent/generic medicines

Alkem's performance is low. It reports no evidence of filing its ten relevant off-patent/generic medicines for registration in access countries, beyond India.

C.2.2 No information on strategies to expand access to off-patent/generic medicines

Alkem's performance is low as it discloses no information on how it expands access to its ten relevant off-patent/generic medicines, beyond India. It does not provide evidence of patient reach and geographic reach.

C.3 No information on strategies to ensure continuous supply

Alkem's performance is low as it discloses no information on how it ensures the continuous supply of its relevant products to access countries, beyond India.

C APPROPRIATE ACCESS & STEWARDSHIP – STEWARDSHIP

Evaluated: stewardship activities relating to antibacterial & antifungal medicines globally

C.4 Educational Stewardship Activities

There is no information regarding Alkem's involvement in AMR-related educational programmes aimed at healthcare professionals and it is therefore not eligible for this indicator as there is no conflict of interest mitigation to be assessed.

C.5 Does not report sales or marketing practices that aim to address appropriate use

Alkem performs low in sales practices. It does not report whether it decouples incentives for sales agents from sales volumes to help prevent the inappropriate use of its antibacterial and/or antifungal medicines.

Alkem does not report to engage in marketing practices that aim to address the appropriate use of its antibacterial and/or antifungal medicines as its marketing materials do not reflect emerging resistance trends or include treatment guidelines for healthcare professionals to raise awareness of AMR and address appropriate use.

C.6 Does not report adapting brochures and/or packaging to facilitate appropriate use by patients

Alkem does not report adapting brochures and/or packaging to facilitate the appropriate use of its antibacterial and/or antifungal medicines by patients.

C.7 AMR Surveillance

As a generic medicine manufacturer, Alkem is not assessed in this indicator nor does it report any involvement in AMR surveillance activities.

† 102 low- and middle-income countries where better access to medicine is most needed.

Overall Performance

2020 2021

31% 71% ▲

Aurobindo Pharma Ltd

Generic medicine manufacturer

Stock exchange: NSE • Ticker: AUROPHARMA • HQ: Hyderabad, India • Employees: 23,000

PERFORMANCE

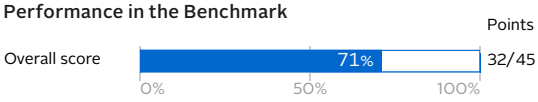
Aurobindo is the leader among the generic medicines manufacturers in scope and performs well in its evaluated Research Areas.

Responsible Manufacturing: Performs well. Reports environmental risk-management strategy for own sites and suppliers; co-leads in reporting compliance with limits at own sites.

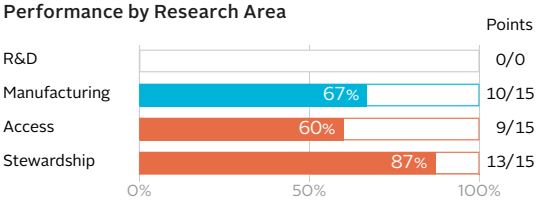
Appropriate Access: Middle-performing. Files its off-patent/generic medicines for registration in access countries. Reports some strategies to expand access and ensure continuous supply of its relevant product.

Stewardship: Performs strongly. It does not promote antibacterial and/or antifungal medicines to healthcare professionals. It reports comprehensive conflict of interest mitigation for its educational programme. It adapts brochures for patients.

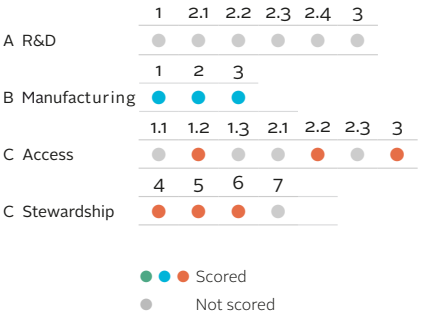
Performance in the Benchmark



Performance by Research Area



How Aurobindo was evaluated



OPPORTUNITIES FOR AUROBINDO

Increase public disclosure on environmental risk management. Aurobindo publishes information on some of the components of its general environmental risk-management strategy. It can publish more information on how it manages environmental risk related to antibiotic discharge in to environment to curb AMR. While Aurobindo reports that all its own sites are compliant with set limits, it can provide clear evidence by publicly disclosing its progress in implementing the strategy and by publishing the audit results of own and suppliers' sites, including antibacterial discharge levels if applicable.

Expand access and ensure adequate supply of antibacterial and antifungal medicines in more access countries. Aurobindo has a Day-1 generic policy by which it introduces a generic product as soon as the patent on a brand expires for the EU and USA. It can expand access to its generic antibiotics and antifungals listed on the 2021 WHO EML to more products and countries, allowing for generic options to be made available in access countries as soon as the originator's patent expires.

Expand adaptations to brochures and packaging to consider more patient needs. In order to support the appropriate use of its antibacterial and/or antifungal medicines by patients, Aurobindo adapts brochures to take account of local languages. It can further adapt its brochures and packaging to consider literacy levels, paediatric use, environmental conditions and patient adherence to treatment.

CHANGES SINCE 2020

- Since 2020, Aurobindo has extended the environmental risk management strategy requirements of its own sites to its suppliers.
- Since 2020, Aurobindo reports that all its own sites that manufacture antibacterials are compliant with discharge limits.
- Aurobindo reports that it fully decouples incentives for sales agents from sales volumes in emerging markets to help prevent the inappropriate use of its antibacterial medicine. It sells antibacterial and antifungal medicines only through tenders in Europe and the US.

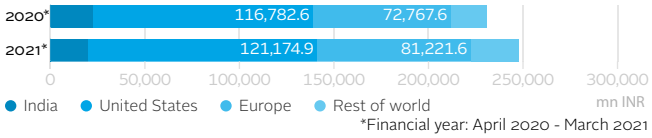
SALES AND OPERATIONS

Therapeutic areas: Anti-allergies, Antibiotics, Anti-diabetics, Anti-retroviral, Cardio-vascular (CVS), Central nervous system (CNS), gastroenterology.
Business segments: Pharmaceuticals (including APIs and formulations)
Product categories: Generic medicines, Biosimilars
M&A since 2020: In February 2020, Aurobindo finalised acquisition of certain Profectus BioSciences Inc assets, including preventative and therapeutic R&D assets to develop vaccine for infectious diseases, for USD 11.29 mn and created a new subsidiary called Auro Vaccines LLC.

Total income by business segment

*Financial year: April 2020 - March 2021

Total income by region



*Financial year: April 2020 - March 2021

PORTFOLIO *for pathogens in scope*

Mid-sized portfolio: At least 39 products: 32 antibacterial medicines; 2 antibacterial vaccines; 5 antifungal medicines
Off-patent/generic medicines: 6 of 39 were selected for analysis* (amoxicillin [A], amoxicillin/clavulanic acid [A], cefuroxime [W], ciprofloxacin [W], fluconazole [F], terbinafine [F])
AWaRe medicines:** 11 Access group; 18 Watch group; 2 Reserve group
Anti-TB medicines:** 1

Products on the market

PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT

As a generic medicine manufacturer, Aurobindo is not evaluated in this Research Area.

B RESPONSIBLE MANUFACTURING Evaluated: antibacterials manufacturing (APIs and drug products)

B.1 Environmental risk-management for own sites and suppliers; tracks compliance with limits at own sites

Aurobindo reports a strategy to minimise the environmental impact of wastewaters and solid waste from antibacterial manufacturing at its sites, including audits at least every five years. It reports setting discharge limits for all antibacterials manufactured at its sites, based on PNECs to limit AMR, as recommended by the AMR Industry Alliance. It also reports quantifying discharge levels at all sites using a mass balance approach, supported by chemical analysis for beta-lactams and cephalosporins. All its 15 sites, of which 4 are ZLD, are reported to be compliant with discharge limits.

Aurobindo requires third-party suppliers of antibacterials to follow the same standards, including audits every five years. It reports procuring around 1% of its antibacterial API volume from 2 supplier sites, which are both ZLD sites. No antibacterial drug products are procured from suppliers.

Aurobindo requires external private and public waste-treatment plants to follow local regulatory standards. It reports auditing the private plants on a yearly basis which includes checking the suitability of technologies used for processing waste and protocols for preventing contamination.

B.2 Publicly discloses some information on environmental risk management

Aurobindo publishes some components of its environmental risk-management strategy. This includes disclosure of the ongoing implementation of necessary processes to deactivate API residues in wastewater. Since 2019, it is a member of the AMR Industry Alliance, which publishes a list of recommended antibacterial discharge targets. Aurobindo publishes that mass balance estimations of antibiotics are conducted. The corresponding results or the discharge levels themselves are not published. Aurobindo also does not publish: (1) the results of environmental audits, whether conducted at its own sites, the sites of suppliers or external private and public waste-treatment plants; (2) a list of these suppliers and plants.

B.3 System in place to maintain production quality for own and suppliers' sites; regulator requested official corrective action

Aurobindo reports that its own sites and suppliers have a system to maintain high-quality antibacterial production consistent with international GMP standards. This includes periodic risk-based audits and tracking of corrective and preventive actions. There is limited information on whether Aurobindo requires its suppliers to audit their own suppliers. In September 2019, an FDA drug quality inspection identified non-conformities with cGMP at one of the company's sites that manufactures antibacterials (Polepally, Mahaboob Nagar, India), resulting in official requests for corrective action. Aurobindo reports that the issue of non-conformities with cGMP have since been resolved with no impact on business continuity, but the regulatory status remains as is because of delays to FDA inspections due to the COVID-19 pandemic.

* See Appendix VII for information about eligibility criteria for products.
** Listed on the 2019 WHO EML.

C APPROPRIATE ACCESS & STEWARDSHIP – ACCESS

Evaluated: access activities relating to antibacterial & antifungal medicines & vaccines in 102 access countries***

Aurobindo is not eligible for indicators: C.1.1, C.1.3, C.2.1 and C.2.3. For more information, see Appendix VII.

C.1.2 Filed to register off-patent/generic medicines in 19 access countries on average

Aurobindo performs above average, filing all its six relevant off-patent/generic medicines for registration in 19 access countries on average. Its most widely filed relevant product is amoxicillin/clavulanic acid filed in 35 access countries. Two of its relevant products are filed in less than 10 access countries. Five of its relevant products are filed for registration in at least one LIC.

C.2.2 Some strategies to expand access to off-patent/generic medicines

Aurobindo has an average performance. It aims to expand access to its off-patent/generic medicines in access countries through affordable prices, tenders and direct sales to its distributors. Between April 2020 and March 2021, Aurobindo estimates to have reached 600,000 patients in Vietnam with its amoxicillin/clavulanic acid generic version.

C.3 Some strategies to ensure continuous supply

Aurobindo has an average performance, with strategies reported in all four areas assessed. It ensures accurate demand planning and data sharing by having a monthly rolling forecast. Aurobindo has a direct-selling model where demand is directly generated by its customers or driven by tenders. Aurobindo mitigates against shortage risks by keeping a buffer stock for its key starting material, APIs and finished products. It reports manufacturing more than 99% of its API in-house. Aurobindo's manufacturing facilities are located in India. It supplies APIs to low- and middle-income countries and aims to improve their capacity to produce finished medicines. To mitigate against substandard and falsified products, it uses security features such as tamper-proof stickers, hot-glue sealing techniques, self-destructing packing materials and serialisation.

C APPROPRIATE ACCESS & STEWARDSHIP – STEWARDSHIP

Evaluated: stewardship activities relating to antibacterial & antifungal medicines globally

C.4 Comprehensive COI mitigation strategies in place for its educational programme

Aurobindo performs strongly in conflict of interest (COI) mitigation for the one AMR-related educational programme for HCPs assessed by the Benchmark. The programme has all three COI mitigation strategies looked for by the Benchmark: (1) content is developed independently from its marketing department; (2) a pledge not to provide financial or material incentives to participants; and (3) a policy of not using branded materials.

C.5 Does not promote its antibacterial and/or antifungal medicines

Aurobindo performs strongly in sales practices. It does not deploy any sales agents to promote its antibacterial and/or antifungal medicines to healthcare professionals. Since Aurobindo does not develop or use marketing materials for antibacterial and/or antifungal medicines to promote such medicines to healthcare professionals, the company is not eligible to be assessed on marketing materials.

C.6 Makes one type of brochure and/or packaging adaptation to facilitate appropriate use by patients

Aurobindo adapts brochures to facilitate the appropriate use of amoxicillin/clavulanic acid by patients. It is middle-performing in this measure, taking account of language. Aurobindo has translated package inserts for amoxicillin/clavulanic acid in Vietnamese.

C.7 AMR Surveillance

As a generic medicine manufacturer, Aurobindo is not assessed in this indicator nor does it report any involvement in AMR surveillance activities.

*** 102 low- and middle-income countries where better access to medicine is most needed.

Overall Performance

2020 2021

70% 60%▼

Cipla Ltd

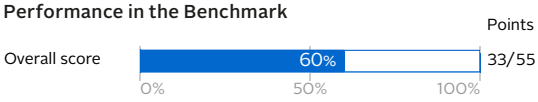
Generic medicine manufacturer

Stock exchange: NSE • Ticker: CIPLA • HQ: Mumbai, India • Employees: 25,672

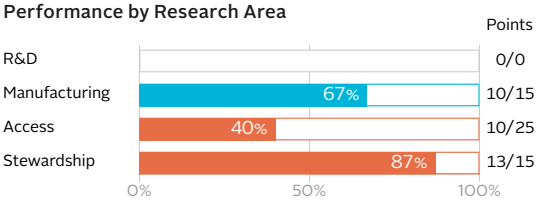
PERFORMANCE

Cipla performs above average overall in its evaluated Research Areas when compared to the other generic medicine manufacturers in scope.
Responsible Manufacturing: Performs well. Reports environmental risk-management strategy for own sites; initial risk assessment of suppliers ongoing.
Appropriate Access: Middle-performing. Filed its on-patent medicine in India. Files some of its off-patent/generic medicines for registration in access countries. Reports some strategies to ensure continuous supply of its relevant product.
Stewardship: Performs strongly. It decouples incentives for sales agents from sales volumes for >99%. It reports comprehensive conflict of interest mitigation for its educational programmes. It adapts brochures and packaging for patients.

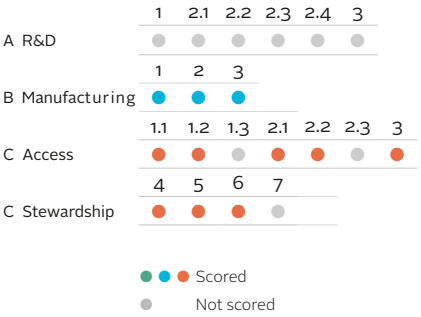
Performance in the Benchmark



Performance by Research Area



How Cipla was evaluated



OPPORTUNITIES FOR CIPLA

Expand environmental risk-management strategy to include suppliers and ensure compliance with limits. Cipla tracks compliance with discharge limits it set for its own manufacturing sites. It can quantify discharge levels at all suppliers' sites and track compliance with limits, and publicly disclose the results. It can also publicly disclose the names and locations of its suppliers and waste-treatment plants for increased transparency.
Expand registration antibacterial medicines to more access countries and ensure adequate supply. Cipla can expand registration of its antibiotics and antifungals listed on the 2021 WHO EML, such as itraconazole and levofloxacin to more countries, including low-income countries and ensure adequate supply. To ensure adequate supply, Cipla can promote capacity building and technology transfer initiatives in access countries, to improve access to its medicines.
Fully decouple incentives for sales agents from sales volumes. Cipla links part of its sales agents' incentives to sales volumes. It can fully decouple incentives for sales agents from sales volumes of antibacterial and antifungal medicines again.

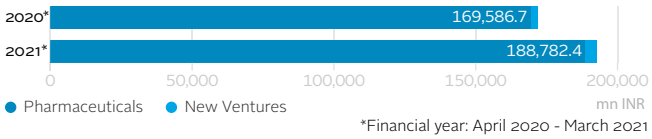
CHANGES SINCE 2020

- As part of the 3-year strategy (2020-2023), Cipla will submit and launch plazomicin in India and other countries, as well as explore multiple opportunities to out-license the product.
- Since 2020, Cipla is in the process of assessing all its suppliers related to the risk of AMR, including requesting data from suppliers on discharge levels.
- Since 2020, Cipla is no longer a member of the AMR Industry Alliance.
- In June 2020, Cipla withdrew its EMA application for a marketing authorisation of plazomicin (Zemdri®), to treat complicated urinary tract infection, due to lack of financial viability.

SALES AND OPERATIONS

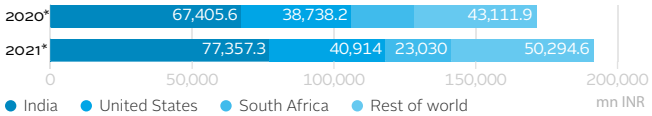
Therapeutic areas: Cardiovascular diseases, Central nervous system, Dermatology, Diagnostics, Gastrointestinal, Infectious diseases, Metabolic disorders, Oncology, Ophthalmology, Orthopaedics, Respiratory diseases, Urology, Women's Health.
Business segments: Pharmaceuticals, New ventures
Product categories: Biosimilars, Consumer health products, Generic medicines, Innovative medicines, Respiratory devices.
M&A since 2020: None in the antibacterial and/or antifungal sectors

Revenue by business segment



*Financial year: April 2020 - March 2021

Revenue by region

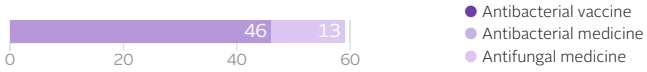


*Financial year: April 2020 - March 2021

PORTFOLIO *for pathogens in scope*

Mid-sized portfolio: At least 59 products: 46 antibacterial medicines; 13 antifungal medicines
On-patent medicine: 1 (plazomicin)
Off-patent/generic medicines: 9 of 58 were selected for analysis* (amoxicillin [A], amoxicillin/clavulanic acid [A], ciprofloxacin [W], colistin [R], fluconazole [F], Fosfomycin [R], itraconazole [F], levofloxacin [W], linezolid [T])
AWaRe medicines:** 5 Access group; 15 Watch group; 8 Reserve group
Anti-TB medicines:** 3

Products on the market



PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT

As a generic medicine manufacturer, Cipla is not evaluated in this Research Area.

B RESPONSIBLE MANUFACTURING Evaluated: antibacterials manufacturing (APIs and drug products)

B.1 Environmental risk-management including limits for own sites; tracks compliance with limits at own sites

Cipla reports a strategy to minimise the environmental impact of wastewaters and solid waste from antibacterial manufacturing at its sites, including audits. It reports setting discharge limits in the receiving environment for all antibacterials manufactured at its sites, based on PNECs to limit AMR, as recommended by the AMR Industry Alliance. Discharge levels are quantified using a mass balance approach, verified by chemical analysis if applicable. It reports three of 10 sites have quantified discharge levels and two, or 20%, of those are compliant with discharge limits. It also reports that the levels of 70% of all antibacterials are quantified and 100% is expected by March 2022.

Cipla will require third-party suppliers of antibacterials to follow similar standards, including limits based on PNECs, after it completes the ongoing initial assessments of all its 57 suppliers. It requests and reviews discharge levels of its suppliers as part of the assessments. It reports 34 of 57 supplier sites, or 60%, are fully assessed but it is unclear how many of the 34 have quantified discharge levels. Complete assessment of all suppliers is expected by March 2022.

There is limited information on the requirements Cipla makes of external private and public waste-treatment plants, in terms of environmental strategy and antibacterial discharge limits. Cipla reports that it requests flow rates from common effluent treatment plants to accurately determine dilution factors and mass balance calculations.

B.2 Publicly discloses some information on environmental risk management and AMR risk identification of own sites

Cipla publishes some components of its environmental risk-management strategy. It publishes that the risk of AMR at all own sites is assessed and priority sites are implementing responsible practices related to AMR. It also publishes that risk assessments of its supplier sites are ongoing. Cipla does not publish: (1) the results of environmental audits, whether conducted at its own sites, the sites of suppliers or external private and public waste-treatment plants; (2) a list of these suppliers and plants; or (3) the limits and levels of antibacterial discharge from its own or suppliers' sites.

B.3 System in place to maintain production quality for own and suppliers' sites; no requests for official corrective action

Cipla reports that its own sites and suppliers have a system to maintain high-quality antibacterial production consistent with international GMP standards. This includes periodic risk-based audits and tracking of corrective and preventive actions. Cipla also requires its suppliers to audit their own suppliers. The Benchmark found no requests for official corrective action from the FDA or EMA related to non-conformities with cGMP at Cipla's own sites or any subsidiaries that manufacture antibacterials.

* See Appendix VII for information about eligibility criteria for products.
** Listed on the 2019 WHO EML.

C APPROPRIATE ACCESS & STEWARDSHIP – ACCESS

Evaluated: access activities relating to antibacterial & antifungal medicines & vaccines in 102 access countries***

Cipla is not eligible for indicators: C.1.3 and C.2.3. For more information, see Appendix VII.

C.1.1 Registration filings for relevant on-patent medicines

Cipla's performance is low as it filed its newly acquired on-patent medicine, the reserve antibiotic plazomicin (Zemdri®) used to treat complicated urinary tract infections, in one access country (India).

C.1.2 Filed to register off-patent/generic medicines in 4 access countries on average

Cipla has an average performance, filing eight of its nine relevant off-patent/generic medicines for registration in six access countries on average. Its most widely filed relevant product is the antifungal fluconazole, filed in 21 access countries. Six of its relevant products are filed in less than 10 access countries. Three of its relevant products are filed for registration in at least one LIC.

C.2.1 Expanding access to on-patent medicines

Cipla 's performance is low as its on-patent medicine, plazomicin, (Zemdri®) is not yet marketed in access countries.

C.2.2 Some strategies to expand access to off-patent/generic medicines

Cipla has an average performance. It reports several examples to demonstrate the number of people who benefitted from its eligible medicines in India and South Africa during the COVID-pandemic peak. For example, Cipla's colistin is available in 500 Indian hospitals and was used to treat 20,000 Indian patients per month. In South Africa, Cipla estimates to have provided access to azithromycin to 280,000 patients. In 2020 and 2021, Cipla participated in a tender to distribute more than 1 mn tablets of Q-TIB, a fixed dose combination used in tuberculosis prevention for people living with HIV, in seven access countries including Haiti, Rwanda and Uganda.

C.3 Some strategies to ensure continuous supply

Cipla has an average performance with strategies reported in three of four areas assessed. It ensures accurate demand planning and data sharing by having a 12-month rolling forecast and conducting long-term demand planning (up to five years). Cipla mitigates against shortage risks by keeping safety stocks and securing sufficient APIs stocks. Cipla does not report capacity building and technology transfer initiatives. To mitigate against substandard and falsified products, Cipla uses an automated Track&Trace system and product or primary packaging serialisation.

C APPROPRIATE ACCESS & STEWARDSHIP – STEWARDSHIP

Evaluated: stewardship activities relating to antibacterial & antifungal medicines globally

C.4 Comprehensive COI mitigation strategies in place for its educational programmes

Cipla performs strongly in the analysis of its top five AMR-related educational programmes for healthcare professionals in conflict of interest (COI) mitigation. All five programmes have all three COI mitigation strategies looked for by the Benchmark: (1) content is developed independently from its marketing department; (2) participants are not provided financial or material incentives; and (3) a policy of not using branded materials.

C.5 Engages in sales and marketing practices to address appropriate use

Cipla performs above average in sales practices. It reports that it partly decouples incentives for sales agents from sales volumes of its antibacterial and/or antifungal medicines. Its percentage of variable pay linked to sales volumes is <1% and sales targets are set at the national level.

Cipla engages in marketing practices that aim to address the appropriate use of its antibacterial and/or antifungal medicines. Its marketing materials reflect emerging resistance trends and/or include treatment guidelines for healthcare professionals: for colistin and itraconazole.

C.6 Makes two types of brochure and/or packaging adaptations to facilitate appropriate use by patients

Cipla adapts brochures and packaging to facilitate the appropriate use of itraconazole, amorolfine, oxiconazole and fosfomycin trometamol by patients. Cipla performs well in this measure, taking account of language and adherence to treatment. It provides packages and leaflets for these products with QR codes that direct patients to information on antifungal resistance in eight to ten regional languages in India. This information aims to improve adherence to treatment.

C.7 AMR Surveillance

As a generic medicine manufacturer, Cipla is not assessed in this indicator but its activities in AMR surveillance are reported. The Benchmark notes that Cipla funds a surveillance programme in the US focused on resistance to plazomicin and has been running since 2018. The programme is an FDA postmarketing requirement and data collection is not complete, therefore data is not yet shared publicly. However, Cipla reports that aggregated results are shared and presented at international infectious disease conferences.

*** 102 low- and middle-income countries where better access to medicine is most needed.

Overall Performance

2020 2021

55% 63%▲

Fresenius Kabi AG

Generic medicine manufacturer

Stock exchange: XFRA • Ticker: FRE (Fresenius SE & Co KGaA)* • HQ: Bad Homburg, Germany • Employees: 40,519

PERFORMANCE

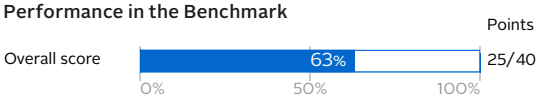
Fresenius Kabi performs above average overall in its evaluated Research Areas when compared to the other generic medicine manufacturers in scope.

Responsible Manufacturing: Middle-performing. Reports environmental risk-management strategy for own sites; limited information on whether AMR and discharge limits are taken into account.

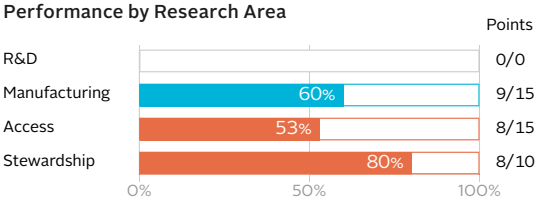
Appropriate Access: Middle-performing. Files some of its off-patent/generic medicines for registration in access countries. Reports some strategies to expand access and ensure continuous supply of its relevant products.

Stewardship: Performs well. It decouples incentives for sales agents from sales volumes by using tender sales for most sales. It reports broad conflict of interest mitigation for its educational programmes.

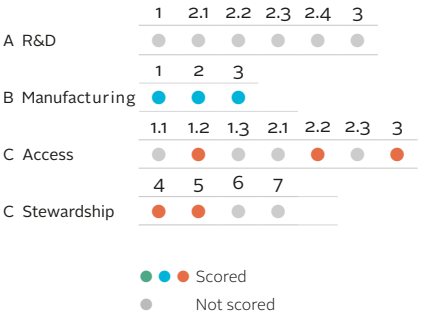
Performance in the Benchmark



Performance by Research Area



How Fresenius Kabi was evaluated



OPPORTUNITIES FOR FRESENIUS KABI

Integrate AMR in environmental risk-management strategy and increase public disclosure. Fresenius Kabi reports an environmental risk management strategy that includes auditing processes and recently became a member of the AMR Industry Alliance. The company can integrate AMR in its strategy for its own manufacturing sites, the sites of suppliers and external private waste-treatment plants, based on the guidelines of the AMR Industry Alliance. This includes setting limits and quantifying discharge levels to track compliance. Moreover, Fresenius Kabi can publish information on how it manages environmental risk related to antibacterial manufacturing to curb AMR. The company currently publishes limited information.

Expand availability and ensure continuous supply of antibacterial and antifungal medicines to more access countries. Fresenius Kabi expands access through direct selling contracts or tenders and reports a set of cost-containment measures. It also reports to ensure accurate demand planning and data sharing. Fresenius Kabi can ensure equitable access and adequate supply of its antibiotics and antifungals listed on the 2021 WHO EML in more access countries. For example, Fresenius Kabi can build on capacity or mitigate against shortages by working with several API suppliers.

Expand registration of antibacterial and antifungal medicines. Fresenius Kabi reports developing generic IV formulations that are ready to launch directly after the patents of the branded products expire. It can apply this policy in access countries and register its antibiotics and antifungals listed on the 2021 WHO EML, (e.g. daptomycin and caspofungin), in more countries, including in low-income countries with a high burden of disease.

CHANGES SINCE 2020

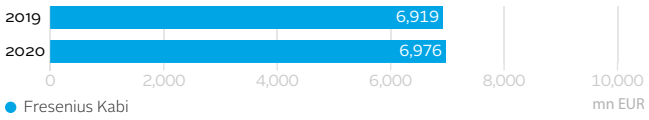
- Fresenius Kabi increased the number of registration filings in access countries for eight out of 10 of its relevant off-patent/generic antibacterial and antifungal medicines, compared to four out of 10 in 2020, meeting the opportunity provided in the 2020 Benchmark. They also increased registration to seven access countries on average from four on average since 2020.
- In 2020, Fresenius Kabi became a member of the AMR Industry Alliance stating a commitment to apply its corresponding guidelines for manufacturing going forward.

* Fresenius Kabi AG is a business segment of Fresenius SE & Co. KGaA

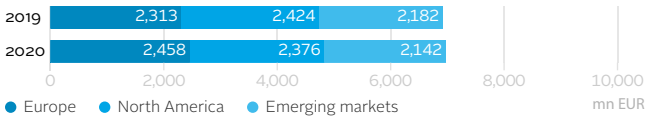
SALES AND OPERATIONS

Therapeutic areas: Anaesthesia, Critical illness, Fluid management, Liver insufficiency, Maldigestion / malabsorption, Oncology, Paediatrics, Transfusion medicine.
Business segments: Fresenius Kabi
Product categories: Biosimilars, Generic medicines, Medical devices
M&A since 2020: None in the antibacterial and/or antifungal sectors

Sales by business segment



Sales by region (Fresenius Kabi)



PORTFOLIO *for pathogens in scope*

Mid-sized portfolio: At least 51 products: 48 antibacterial medicines; 3 antifungal medicines
Off-patent/generic medicines: 10 of 51 were selected for analysis** (aztreonam [R], caspofungin [F], clindamycin [A], daptomycin [R], fluconazole [F], isoniazid [T], linezolid [T], meropenem [W], metronidazole [A], piperacillin/tazobactam [W])
AWaRe medicines*:** 16 Access group; 22 Watch group; 5 Reserve group
Anti-TB medicines*:** 3

Products on the market

PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT

As a generic medicine manufacturer, Fresenius Kabi is not evaluated in this Research Area.

B RESPONSIBLE MANUFACTURING Evaluated: antibacterials manufacturing (APIs and drug products)

B.1 Environmental risk-management for own sites; questionnaire-based assessments of all suppliers

Fresenius Kabi reports a strategy to minimise the environmental impact of wastewaters and solid waste from antibacterial manufacturing at its sites, including audits every 1-4 years. It became a member of the AMR Industry Alliance in 2020 and plans to set discharge limits and quantify levels at its sites in the near future.

There is limited information on the requirements that Fresenius Kabi makes of third-party suppliers of antibacterials with respect to AMR. It reports conducting a questionnaire-based CSR assessment of all suppliers which includes questions on how antibacterial waste is processed by suppliers. It does not report requiring suppliers to set discharge limits or quantify discharge levels.

There is also limited information on the requirements Fresenius Kabi makes of external private and public waste-treatment plants, in terms of environmental strategy, audits and antibacterial discharge limits and levels. It reports external waste disposal companies are regularly audited but exact audit parameters are defined locally by each site.

B.2 Publicly discloses some information on environmental risk management

Fresenius Kabi publishes some components of its environmental risk-management strategy, without specific references to AMR. It does publicly disclose that non-recyclable hazardous waste including antibiotics is mainly incinerated. Since 2020, it is a member of the AMR Industry Alliance, which publishes a list of recommended antibacterial discharge targets. Fresenius Kabi does not publish: (1) the results of environmental audits, whether conducted at its own sites, the sites of suppliers or external private and public waste-treatment plants; (2) a list of these suppliers and plants; or (3) the levels of antibacterial discharge from its own or suppliers' sites.

B.3 System in place to maintain production quality for own and suppliers' sites; no requests for official corrective action

Fresenius Kabi reports own sites and suppliers have a system to maintain high-quality antibacterial production consistent with international GMP standards. This includes periodic risk-based audits and tracking of corrective and preventive actions. It also reviews, as part of its external audit process, the results of audits that suppliers conducted with their own suppliers. The Benchmark found no requests for official corrective action from the FDA or EMA related to non-conformities with cGMP at Fresenius Kabi's own sites or any subsidiaries that manufacture antibacterials.

** See Appendix VII for information about eligibility criteria for products.
*** Listed on the 2019 WHO EML.

C APPROPRIATE ACCESS & STEWARDSHIP – ACCESS

Evaluated: access activities relating to antibacterial & antifungal medicines & vaccines in 102 access countries†

Fresenius Kabi is not eligible for indicators: C.1.1, C.1.3, C.2.1 and C.2.3. For more information, see Appendix VII.

C.1.2 Filed to register off-patent/generic medicines in 7 access countries on average

Fresenius Kabi has an average performance, filing eight of its 10 relevant off-patent/generic medicines for registration in seven access countries on average. Its most widely filed relevant product is the antifungal metronidazole filed in 21 access countries. Seven of its relevant products are filed in less than ten access countries. Two of its relevant products are filed for registration in at least one LIC.

C.2.2 Some strategies to expand access to off-patent/generic medicines

Fresenius Kabi has an average performance. It expands access to its off-patent/generic medicines in access countries through direct sales contracts or tenders. Fresenius Kabi reports a set of cost-containment measures applied on its generic medicines, leading to lower prices. It provides some evidence of patient reach. Details were provided under the basis of confidentiality.

C.3 Some strategies to ensure continuous supply

Fresenius Kabi has an average performance, with strategies reported in all four areas assessed. It ensures accurate demand planning and data sharing and mitigates against shortages risks. Details were provided under the basis of confidentiality. It conducts internal or external audits of its suppliers, ensures compliance to the ISO and GMP standards, evaluates its supply performance through KPIs and has a Supplier Code of Conduct. Fresenius Kabi reports, subject to confidentiality, where it produces antibiotics in low- and middle-income countries. To mitigate against substandard and falsified products, Fresenius Kabi has implemented a Global Serialisation Program.

C APPROPRIATE ACCESS & STEWARDSHIP – STEWARDSHIP

Evaluated: stewardship activities relating to antibacterial & antifungal medicines globally

C.4 Broad COI mitigation strategies in place for its educational programmes

Fresenius Kabi performs well in conflict of interest (COI) mitigation for the five AMR-related educational programmes for HCPs assessed by the Benchmark. Four programmes have all three COI mitigation strategies looked for by the Benchmark: (1) content is developed independently from its marketing department; (2) a pledge not to provide financial or material incentives to participants; and (3) a policy of not using branded materials. The remaining programme has two COI mitigation strategies: the content is developed by Fresenius Kabi's marketing department.

C.5 Engages in sales and marketing practices to address appropriate use

Fresenius Kabi performs above average in sales practices. It reports that it sells most of its antibacterial and/or antifungal medicines through hospital tenders and does not have sales incentives linked to the sales volume of these tenders.

Fresenius Kabi engages in marketing practices that aim to address the appropriate use of its antibacterial and/or antifungal medicines. Its marketing materials include emerging resistance trends and/or include treatment guidelines for healthcare professionals: for a range of its intravenous antibacterial medicines used in intensive care units.

C.6 Stewardship-Oriented Adaptations for Patients

Fresenius Kabi is not eligible for this indicator as its medicines are administered by healthcare professionals in the hospital setting so there is no need to adapt brochures and/or packaging to facilitate the appropriate use of its antibacterial and/or antifungal medicines by patients.

C.7 AMR Surveillance

As a generic medicine manufacturer, Fresenius Kabi is not assessed in this indicator nor does it report any involvement in AMR surveillance activities.

† 102 low- and middle-income countries where better access to medicine is most needed.

Overall Performance

2020	2021
6%	15% ▲

Hainan Hailing Chemipharma Corp Ltd

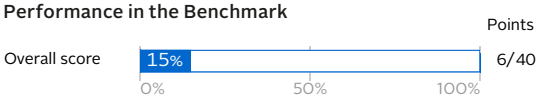
Generic medicine manufacturer

Stock exchange: Privately held • Ticker: N/A • HQ: Haikou, China • Employees: 600

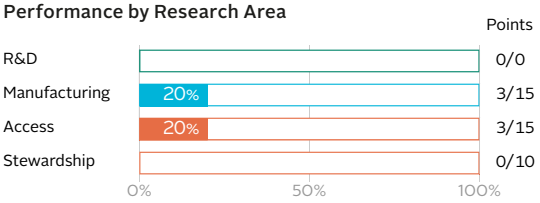
PERFORMANCE

Hainan Hailing performs low overall in its evaluated Research Areas when compared to the other generic medicine manufacturers in scope.
Responsible Manufacturing: Performs low. Reports a general environmental risk-management strategy but without a specific aim to limit AMR.
Appropriate Access: Performs low. Discloses no information on registration filings, expanding access or ensuring continuous supply for its off-patent/generic medicines.
Stewardship: Performs low. It does not report decoupling incentives for sales agents from sales volumes. It does not adapt brochures or packaging for patients.

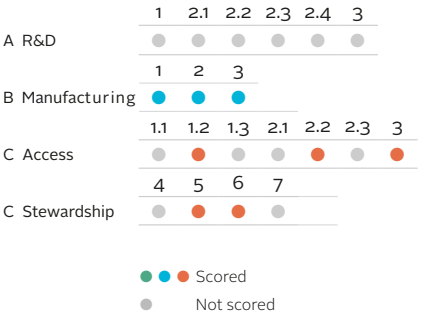
Performance in the Benchmark



Performance by Research Area



How Hainan Hailing was evaluated



OPPORTUNITIES FOR HAINAN HAILING

Develop an AMR-specific environmental risk-management strategy and increase public disclosure. Hainan Hailing reports a commitment to manufacture its products in an environmentally responsible manner without specifying whether AMR is taken into account. The company can develop an AMR strategy for its own manufacturing sites, the sites of suppliers and external private waste-treatment plants, based on the guidelines of the AMR Industry Alliance. This includes setting limits and quantifying discharge levels to track compliance. Moreover, Hainan Hailing can publish information on how it manages environmental risk related to antibacterial manufacturing to curb AMR. The company currently publishes limited information.
Expand registration and ensure availability of antibacterial and antifungal medicines. Hainan Hailing can expand registration and ensure equitable access of its antibiotics and antifungals listed on the 2021 WHO EML, such as cefepime and ceftazidime, to more countries, including low-income countries. It can improve transparency on where its medicines are registered and made available.
Apply responsible sales practices for antibacterial and antifungal medicines. Hainan Hailing can apply responsible sales practices for antibacterial and antifungal medicines by not deploying sales agents. Alternatively, it can fully decouple incentives for sales agents from sales volumes of such medicines.

CHANGES SINCE 2020

No changes are reported for Hainan Hailing.

* All companies were assessed based on data submitted to the Benchmark in the current and previous periods of analysis, as well as information the companies have made publicly available, or that are accessible through other sources. For the 2021 Benchmark, Hainan Hailing declined to submit data to the Antimicrobial Resistance Benchmark.

SALES AND OPERATIONS

Therapeutic areas: Antifungal, Anti-infective, Angyomyocardiac, Anti-diabetics, Gastrointestinal, Nervous system
Business segments: Pharmaceuticals
Product categories: Generic medicines
M&A since 2020: None in the antibacterial and/or antifungal sectors

Revenue by business segment

Revenue by region

PORTFOLIO *for pathogens in scope*

Mid-sized portfolio: At least 43 products: 41 antibacterial medicines; 2 antifungal medicines
Off-patent/generic medicines: 8 of 43 were selected for analysis** (amoxicillin [A], amoxicillin/clavulanic acid [A], caspofungin [F], cefepime [W], ceftazidime [W], faropenem [R], luliconazole [F], rifandine [T])
AWaRe medicines*:** 11 Access group; 25 Watch group; 1 Reserve group
Anti-TB medicines*:** 1

Products on the market

PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT

As a generic medicine manufacturer, Hainan Hailing is not evaluated in this Research Area.

B RESPONSIBLE MANUFACTURING Evaluated: antibacterials manufacturing (APIs and drug products)

B.1 No AMR-specific environmental risk-management strategy

Hainan Hailing states a general commitment to manufacture its products in an environmentally responsible manner, supported by a discharge monitoring system to ensure compliance with local regulations. It is unclear how the strategy takes AMR into account or aims to minimise the environmental impact of wastewaters and solid waste from antibacterial manufacturing at its own sites, third-party suppliers of antibacterials or external private and public waste-treatment plants.

B.2 Limited publicly available information on environmental risk management

Hainan Hailing publishes limited information on its approach to environmental risk-management, without specific references to AMR. It does not publish: (1) the results of environmental audits, whether conducted at its own sites, the sites of suppliers or external private and public waste-treatment plants; (2) a list of these suppliers and plants; or (3) the limits and levels of antibacterial discharge from its own or suppliers' sites.

B.3 System in place to maintain production quality for own sites; limited information on suppliers; no requests for official corrective action

Hainan Hailing reports that its own sites have a system to maintain high-quality antibacterial production consistent with international GMP standards. There is limited information on audits, corrective actions and on how the company ensures that its suppliers uphold quality standards comparable to its own. The Benchmark found no requests for official corrective action from the FDA or EMA related to non-conformities with cGMP at Hainan Hailing's own sites or any subsidiaries.

** See Appendix VII for information about eligibility criteria for products.
*** Listed on the 2019 WHO EML.

C APPROPRIATE ACCESS & STEWARDSHIP – ACCESS

Evaluated: access activities relating to antibacterial & antifungal medicines & vaccines in 102 access countries†

Hainan Hailing is not eligible for indicators: C.1.1, C.1.3, C.2.1 and C.2.3 For more information, see Appendix VII.

C.1.2 No information on registration filings for off-patent/generic medicines

Hainan Hailing's performance is low, as it reports no evidence of filing its eight relevant off-patent/generic medicines for registration in access countries, beyond China.

C.2.2 No information on strategies to expand access to off-patent/generic medicines

Hainan Hailing's performance is low, as it discloses no information on how it expands access to its eight relevant off-patent/generic medicines, beyond China. It does not provide evidence of patient and geographic reach.

C.3 No information on strategies to ensure continuous supply

Hainan Hailing's performance is low, as it discloses no information on how it ensures the continuous supply of its relevant products to access countries, beyond China.

C APPROPRIATE ACCESS & STEWARDSHIP – STEWARDSHIP

Evaluated: stewardship activities relating to antibacterial & antifungal medicines globally

C.4 Educational Stewardship Activities

There is no information regarding Hainan Hailing's involvement in AMR-related educational programmes aimed at healthcare professionals and it is therefore not eligible for this indicator as there is no conflict of interest mitigation to be assessed.

C.5 Does not report sales or marketing practices that aim to address appropriate use

Hainan Hailing performs low in sales practices. It does not report whether it decouples incentives for sales agents from sales volumes to help prevent the inappropriate use of its antibacterial and/or antifungal medicines.

Hainan Hailing does not report to engage in marketing practices that aim to address the appropriate use of its antibacterial and/or antifungal medicines as its marketing materials do not reflect emerging resistance trends or include treatment guidelines for healthcare professionals to raise awareness of AMR and address appropriate use.

C.6 Does not report adapting brochures and/or packaging to facilitate appropriate use by patients

Hainan Hailing does not report adapting brochures and/or packaging to facilitate the appropriate use of its antibacterial and/or antifungal medicines by patients.

C.7 AMR Surveillance

As a generic medicine manufacturer, Hainan Hailing is not assessed in this indicator nor does it report any involvement in AMR surveillance activities.

† 102 low- and middle-income countries where better access to medicine is most needed.

Overall Performance

2020	2021
11%	47% ▲

Sun Pharmaceutical Industries Ltd

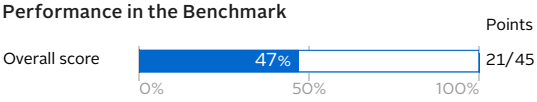
Generic medicine manufacturer

Stock exchange: NSE • Ticker: SUNPHARMA • HQ: Mumbai, India • Employees: 36,000

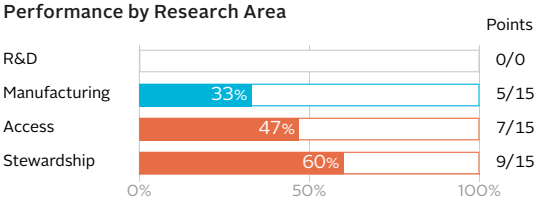
PERFORMANCE

Sun Pharma performs average overall in its evaluated Research Areas when compared to the other generic medicine manufacturers in scope.
Responsible Manufacturing: Performs low. Reports a general environmental risk-management strategy but without a specific aim to limit AMR.
Appropriate Access: Middle-performing. Files its off-patent products in access countries. Discloses some strategies to expand access and ensure continuous supply of its off-patent products.
Stewardship: Middle-performing. It does not report decoupling incentives for sales agents from sales volumes. It reports comprehensive conflict of interest mitigation for its educational programme. It adapts brochures and/or packaging for patients.

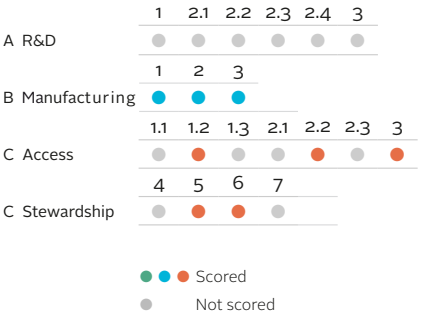
Performance in the Benchmark



Performance by Research Area



How Sun Pharma was evaluated



OPPORTUNITIES FOR SUN PHARMA

Develop an AMR-specific environmental risk-management strategy and increase public disclosure. Sun Pharma reports a commitment to manufacture its products in an environmentally responsible manner without specifying whether AMR is taken into account. It reports having one owned manufacturing site, which employs Zero Liquid Discharge (ZLD) treatment processes. The company can develop an AMR strategy for its own site and suppliers, based on the guidelines of the AMR Industry Alliance. This includes setting limits and quantifying discharge levels to track compliance. Sun Pharma can publish information on how it manages environmental risk related to antibacterial manufacturing. The company publishes limited information about this.
Expand availability and ensure conitinuous supply of antibacterial and antifungal medicines to more access countries. Sun Pharma can ensure equitable access and adequate supply of its antibiotics and antifungals listed on the 2021 WHO EML (e.g. the antifungal itraconazole and the reserve antibiotic tigecycline) in more access countries. For example, Sun Pharma can ensure accurate demand planning and data sharing, build on capacity or mitigate against shortages by working with several API suppliers.
Apply responsible sales practices for antibacterial and antifungal medicines. Sun Pharma can apply responsible sales practices for antibacterial and antifungal medicines by not deploying sales agents. Alternatively, it can fully decouple incentives for sales agents from sales volumes of such medicines.

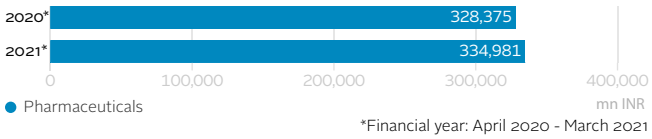
CHANGES SINCE 2020

No changes are reported for Sun Pharma.

SALES AND OPERATIONS

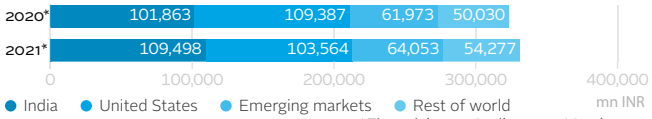
Therapeutic areas: Anti-infectives, Cardiology, Dental, Dermatology, Diabetology, Gastroenterology, Gynaecology, Nephrology, Neurology, Nutritionals, Oncology, Ophthalmology, Orthopaedic, Psychiatry, Respiratory, Urology
Business segments: Pharmaceuticals
Product categories: Consumer health products, Generic medicines, Innovative medicines
M&A since 2020: None in the antibacterial and/or antifungal sectors

Total income by business segment



*Financial year: April 2020 - March 2021

Total income by region



*Financial year: April 2020 - March 2021

PORTFOLIO *for pathogens in scope*

Mid-sized portfolio: At least 52 products: 44 antibacterial medicines; 8 antifungal medicines
Off-patent/generic medicines: 8 of 52 were selected for analysis* (amoxicillin [A], amoxicillin/clavulanic acid [A], ciprofloxacin [W], colistin [R], itraconazole [F], levofloxacin [W], nystatin [F], tigecycline [R])
AWaRe medicines:** 9 Access group; 19 Watch group; 3 Reserve group

Products on the market

PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT

As a generic medicine manufacturer, Sun Pharma is not evaluated in this Research Area.

B RESPONSIBLE MANUFACTURING Evaluated: antibacterials manufacturing (APIs and drug products)

B.1 No AMR-specific environmental risk management strategy; ZLD at own site

Sun Pharma reports a commitment to manufacture its products in an environmentally responsible manner, supported by a management system that includes periodic audits. It is unclear how the strategy takes AMR into account or aims to minimise the environmental impact of wastewaters and solid waste from antibacterial manufacturing at its own site, third-party suppliers of antibacterials or external private and public waste-treatment plants. Sun Pharma does report that its sole site that manufactures antibacterials is ZLD implying that no liquid waste is discharged into the environment from this site. It also reports that any antibacterial residue from ZLD is sent for incineration.

B.2 Limited publicly available information on environmental risk management

Sun Pharma publishes limited information on its approach to environmental risk-management, without specific references to AMR. It publishes that any manufacturing site that manufactures antibiotics is qualified as ZLD. It does not publish: (1) the results of environmental audits, whether conducted at its own site, the sites of suppliers or external private and public waste-treatment plants; (2) a list of these suppliers and plants; or (3) the limits and levels of antibacterial discharge from its own or suppliers' sites.

B.3 System in place to maintain production quality for own sites; no requests for official corrective action

Sun Pharma publicly discloses that its own site has a system, including audits, to maintain high-quality antibacterial production, consistent with international GMP standards. It reports auditing its suppliers on quality standards as well. There is limited information on how corrective actions are implemented and tracked. The Benchmark found no requests for official corrective action from the FDA or EMA related to non-conformities with cGMP at Sun Pharma's own sites or any subsidiaries that manufacture antibacterials.

* See Appendix VII for information about eligibility criteria for products.
** Listed on the 2019 WHO EML.

C APPROPRIATE ACCESS & STEWARDSHIP – ACCESS

Evaluated: access activities relating to antibacterial & antifungal medicines & vaccines in 102 access countries***

Sun Pharma is not eligible for indicators: C.1.1, C.1.3, C.2.1 and C.2.3. For more information, see Appendix VII.

C.1.2 Filed to register off-patent/generic medicines in 8 access countries on average

Sun Pharma has an average performance, filing all its 8 relevant off-patent/generic medicines for registration in 8 access countries on average. Its most widely filed relevant product is the antibiotic amoxicillin/clavulanic acid filed in 22 access countries. Four of its relevant products are filed for registration in at least one LIC.

C.2.2 Some strategies to expand access to off-patent/generic medicines

Sun Pharma has an average performance. It reports providing access to its antibiotics and antifungals to 45 access countries, of which low-income countries such as Chad, Nepal and Syria. In 2020, Sun Pharma estimates to have provided access to its amoxicillin/clavulanic acid to 890,000 patients in 19 access countries, including Cameroon, Myanmar, and Peru.

C.3 Some strategies to ensure continuous supply

Sun Pharma has an average performance with strategies reported in three of four areas assessed. It reports complying with good manufacturing practices when producing API and drug products. Sun Pharma works towards product accessibility by ensuring regular supply of its products and having a robust distribution network in India, where it supplied its medicines to more than 500,000 pharmacies in urban and rural areas in 2020. Sun Pharma does not report capacity building and technology transfer initiatives. It mitigates against falsified and substandard medicines by reporting any suspicion of counterfeit to the approriate regulatory authorities. It uses a 'Track and Trace' technology to prevent the sale of counterfeit medicines and to ensure the authenticity of its products. Sun Pharma has a dedicated task force in place to train filed forces to identify counterfeits.

C APPROPRIATE ACCESS & STEWARDSHIP – STEWARDSHIP

Evaluated: stewardship activities relating to antibacterial & antifungal medicines globally

C.4 Comprehensive COI mitigation strategies in place for its educational programmes

Sun Pharma performs strongly in conflict of interest (COI) mitigation for the five AMR-related educational programme for HCPs assessed by the Benchmark. To mitigate COI for all five programmes, it provides financial resources to independent third parties (DocMode, KOL International Academy, Mediquest and Mindsync) to develop the programmes.

C.5 Does not report sales or marketing practices that aim to address appropriate use

Sun Pharma performs low in sales practices. It does not report whether it decouples incentives for sales agents from sales volumes to help prevent the inappropriate use of its antibacterial and/or antifungal medicines.

Sun Pharma does not report to engage in marketing practices that aim to address the appropriate use of its antibacterial and/or antifungal medicines as its marketing materials do not reflect emerging resistance trends or include treatment guidelines for healthcare professionals to raise awareness of AMR and address appropriate use.

C.6 Makes two types of brochure and/or packaging adaptations to facilitate appropriate use by patients

Sun Pharma adapts brochures and/or packaging to facilitate the appropriate use of amoxicillin/clavulanic acid by patients. Sun Pharma performs well in this measure, taking account of language and adherence to treatment. It has created a QR code which directs to information on how to take the product appropriately translated in ten regional languages in India. It also adapts packaging to include information on AMR and how to take the product appropriately.

C.7 AMR Surveillance

As a generic medicine manufacturer, Sun Pharma is not assessed in this indicator nor does it report any involvement in AMR surveillance activities.

*** 102 low- and middle-income countries where better access to medicine is most needed.

Overall Performance

2020 2021

63% 60%▼

Teva Pharmaceutical Industries Ltd

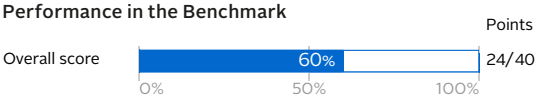
Generic medicine manufacturer

Stock exchange: NYSE • Ticker: TEVA • HQ: Petah Tikva, Israel • Employees: 40,216

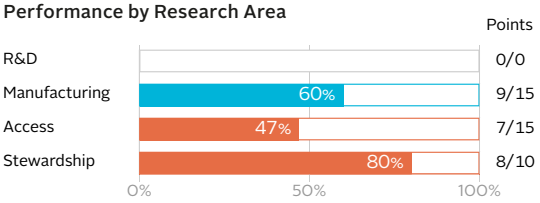
PERFORMANCE

Teva performs above average overall in its evaluated Research Areas when compared to the other generic medicine manufacturers in scope.
Responsible Manufacturing: Middle-performing. Reports environmental risk-management strategy for own sites; tracks compliance with limits at own sites.
Appropriate Access: Middle-performing. Files some of its relevant products (off-patent generic medicines) for registration in access countries. Reports some strategies to expand access and ensure continuous supply of its relevant product.
Stewardship: Performs well. It does not promote antibacterial and/or antifungal medicines to healthcare professionals. It adapts packaging for patients.

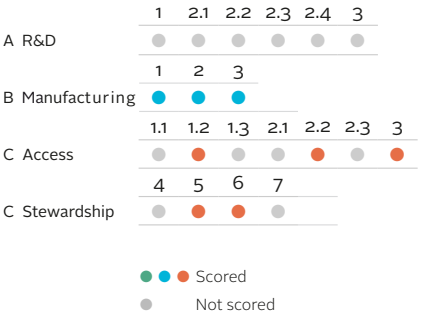
Performance in the Benchmark



Performance by Research Area



How Teva was evaluated



OPPORTUNITIES FOR TEVA

Ensure compliance with antibacterial discharge limits at suppliers sites by tracking and publicly disclosing progress and results specific to antibacterials for all sites. Teva can set limits and quantify discharge levels to track compliance at all suppliers's sites, as it does at its own sites, and publicly disclose the results. Teva reports the goal to audit half of all supplier sites by end of 2030. Teva can also publish information on how it manages environmental risk related to antibacterial manufacturing. The company currently publishes limited information.
Expand registration of antibacterial and antifungal medicines. Teva can expand registration of its antibiotics and antifungals listed on the 2021 WHO EML, such as cefalexin, colistin and nystatin, to more countries, including low-income countries.
Ensure continuous supply of antibacterial and antifungal medicines. Teva mitigates against shortage risks, e.g., by maintaining a flexible safety stock management process and keeping buffer stocks. It can implement several strategies to mitigate against shortage risks in access countries, e.g., build local manufacturing capacity and transfer technology into access countries.
Expand adaptations to brochures and packaging to consider more patient needs. In order to support the appropriate use of its antibacterial and/or antifungal medicines by patients, Teva adapts brochures to take account of local languages. It can further adapt its brochures and packaging to consider literacy levels, paediatric use, environmental conditions and patient adherence to treatment.

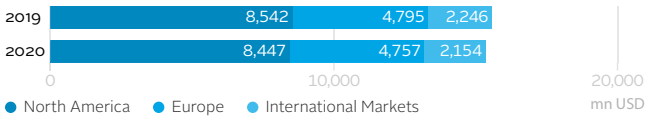
CHANGES SINCE 2020

- In its 2020 Environmental, Social and Governance (ESG) Progress Report, Teva publicly commits to meet existing AMR Industry Alliance commitments to minimise antimicrobial discharges from its own operations and supply chain by 2030.
- Teva pledged an unknown amount to the AMR Action Fund

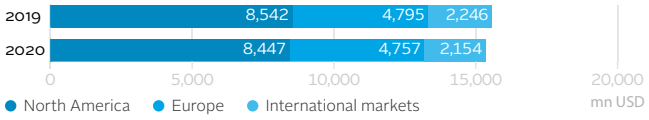
SALES AND OPERATIONS

Therapeutic areas: Migraine/headache/pain, Neurodegenerative conditions and movement disorders, Oncology, Respiratory
Business segments: North America, Europe, International Markets
Product categories: Biosimilars, Generic medicines, Innovative medicines
M&A since 2020: None in the antibacterial and/or antifungal sectors

Net revenues by business segment



Net revenues by region



PORTFOLIO *for pathogens in scope*

Comparatively large portfolio: At least 137 products: 115 antibacterial medicines; 22 antifungal medicines
Off-patent/generic medicines: 10 of 137 were selected for analysis* (amoxicillin [A], azithromycin [W], cefalexin [A], ciprofloxacin [W], clotrimazole [F], colistin [R], daptomycin [R], ethambutol [T], isoniazid [T], nystatin [F])
AWaRe medicines:** 21 Access group; 43 Watch group; 5 Reserve group
Anti-TB medicines:** 4

Products on the market

PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT

As a generic medicine manufacturer, Teva is not evaluated in this Research Area.

B RESPONSIBLE MANUFACTURING Evaluated: antibacterials manufacturing (APIs and drug products)

B.1 Environmental risk-management for own sites and plans implementation at supplier sites

Teva reports a strategy to minimise the environmental impact of wastewaters and solid waste from antibacterial manufacturing at its sites, including audits every three years. It reports setting discharge limits in the receiving environment for all antibacterials manufactured at its sites, based on PNECs to limit AMR, as recommended by the AMR Industry Alliance. Discharge levels are quantified using a mass balance approach. It reports 22 of 32 sites have quantified discharge levels and 10, or 31%, are compliant with discharge limits.

Teva started requiring third-party suppliers of antibacterials to follow similar standards. It reports a goal to audit 50% of all >250 suppliers by the end of 2030.*** It does not yet require suppliers to set discharge limits or quantify discharge levels.

Teva expects external public and private waste treatment plants to comply with its general environmental standards. There is limited information on the requirements Teva makes of external private and public waste-treatment plants, in terms of audits and antibacterial discharge limits and levels.

B.2 Publicly discloses some information on environmental risk management and quantifying discharge levels at own sites

Teva publishes some components of its environmental risk-management strategy. It is a member of the AMR Industry Alliance, which publishes a list of recommended antibacterial discharge targets. Teva publicly commits to quantifying discharge levels at 20 of its 34 own sites that manufacture antimicrobials by the end of 2020.† The levels themselves are not published. Teva also does not publish: (1) the results of environmental audits, whether conducted at its own sites, the sites of suppliers or external private and public waste-treatment plants; or (2) a list of these suppliers and plants.

B.3 System in place to maintain production quality for own and suppliers' sites; regulator requested official corrective action

Teva reports that its own sites and suppliers have a system to maintain high-quality antibacterial production consistent with international GMP standards. This includes periodic risk-based audits and tracking of corrective and preventive actions. There is limited information on whether Teva requires its suppliers to audit their own suppliers. In January 2020, an FDA drug quality inspection identified non-conformities with cGMP at one Actavis site (a Teva subsidiary in Davie, FL, USA) producing antibacterial drug

* See Appendix VII for information about eligibility criteria for products.
** Listed on the 2019 WHO EML.
***After period of analysis, Teva reported that the number of suppliers is updated to ~150.
†Discrepancy with number of sites in B.1 is explained by Teva's submission data for the Benchmark being more up to date than publicly available data.

products, resulting in an official request for corrective action. Teva reports that the oral antibacterial products manufactured at this site were not impacted by the observations and that the site is taking corrective actions.

C APPROPRIATE ACCESS & STEWARDSHIP – ACCESS

Evaluated: access activities relating to antibacterial & antifungal medicines & vaccines in 102 access countries‡

Teva is not eligible for indicators: C.1.1, C.1.3, C.2.1 and C.2.3. For more information, see Appendix VII.

C.1.2 Filed to register off-patent/generic medicines in 3 access countries on average

Teva has an average performance, filing three of its 10 relevant off-patent/generic medicines for registration in three access countries on average. Its most widely filed relevant product is the antibacterial azithromycin, filed in 19 access countries. Two of its relevant products are filed in less than ten access countries. One of its relevant product (azithromycin) is filed for registration in seven LICs.

C.2.2 Some strategies to expand access to off-patent/generic medicines

Teva has an average performance, with access strategies reported for three of its ten relevant off-patent/generic medicines. It aims to expand access in access countries through donations and tenders. In 2020, Teva, together with its partners, reports having donated more than 17 mn units of antibiotics and antifungals to access countries. In Malawi, Teva is partnering with Global HOPE and Direct Relief, to donate antibiotics for pediatric immunosuppressed cancer patients. The initiative aims to treat 4,000 new patients in Malawi over the next five years. Teva participates to the GDF and IDA Foundation global tenders for tuberculosis, to provide linezolid to all GDF eligible countries.

C.3 Some strategies to ensure continuous supply

Teva has an average performance, with strategies reported in three of four areas assessed. Teva mitigates against shortage risks by maintaining a certain volume of products ready to donate. Teva has a flexible safety stock management process within its Enterprise Resource Planning (ERP) system. It reports keeping buffer stocks. Teva does not report capacity building and technology transfer initiatives. To mitigate against substandard and falsified products, Teva directly donates its medicines to certified partners and uses security features such as serialisation.

C APPROPRIATE ACCESS & STEWARDSHIP – STEWARDSHIP

Evaluated: stewardship activities relating to antibacterial & antifungal medicines globally

C.4 Educational Stewardship Activities

There is no information regarding Teva's involvement in AMR-related educational programmes aimed at healthcare professionals and it is therefore not eligible for this indicator as there is no conflict of interest mitigation to be assessed.

C.5 Does not promote its antibacterial and/or antifungal medicines

Teva performs strongly in sales practices. It does not deploy any sales agents to promote its antibacterial and/or antifungal medicines to healthcare professionals. Since Teva does not develop or use marketing materials for antibacterial and/or antifungal medicines to promote such medicines to healthcare professionals, the company is not eligible to be assessed on marketing materials.

C.6 Makes one type of brochure and/or packaging adaptation to facilitate appropriate use by patients

Teva adapts packaging to facilitate the appropriate use of azithromycin, linezolid and pyridoxine by patients. Teva is middle-performing in this measure, taking account of language. The packaging contains information translated into English, Spanish, French and/or Portuguese.

C.7 AMR Surveillance

As a generic medicine manufacturer, Teva is not assessed in this indicator nor does it report any involvement in AMR surveillance activities.

‡ 102 low- and middle-income countries where better access to medicine is most needed.

Overall Performance

2020 2021

53% 67% ▲

Viatris Inc

Generic medicine manufacturer

Stock exchange: NASDAQ • Ticker: VTRS • HQ: Canonsburg, PA, US • Employees: 45,000

PERFORMANCE

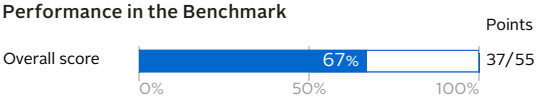
Viatris performs well overall in its evaluated Research Areas compared to the other generic medicine manufacturers in scope.

Responsible Manufacturing: Performs well. Reports environmental risk-management strategy for own sites and suppliers; co-leads in reporting compliance with limits at own sites.

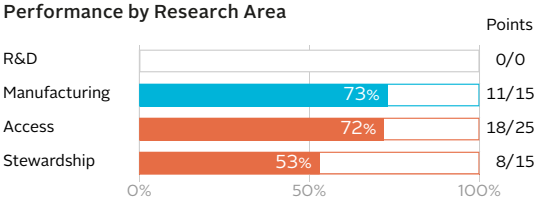
Appropriate Access: Performs strongly. Files some of its on- and off-patent products for registration in access countries. Reports several strategies to expand access and ensure continuous supply of its relevant products.

Stewardship: Middle-performing. It does not promote two products to healthcare professionals, however it does not decouple sales incentives from sales volumes for its other products. It reports comprehensive conflict of interest mitigation for its educational programmes. It does not adapt brochures or packaging for patients.

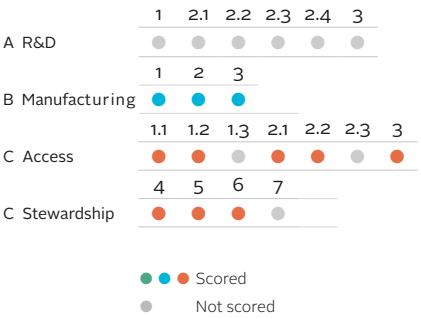
Performance in the Benchmark



Performance by Research Area



How Viatris was evaluated



OPPORTUNITIES FOR VIATRIS

Ensure compliance with antibacterial discharge limits at suppliers' sites by tracking and publicly disclosing progress and results specific to antibacterials for all sites. Viatris can set limits and quantify discharge levels to track compliance at all suppliers' sites and it can publicly disclose the results. Viatris can also publish information on how it manages environmental risk related to antibacterial manufacturing. To provide clear evidence of its progress it can publicly report compliance at all sites. Disclosure of information, including the results of audits and antibacterial discharge levels of its own sites and suppliers' sites, is important. It can also publicly disclose the names and locations of its suppliers and waste-treatment plants for increased transparency.

Improve accessibility of pretomanid (Dovprela) and delamanid (Deltyba®). Viatris filed delamanid (Deltyba®) and pretomanid (Dovprela) for registration in seven and 23 access countries. It can expand the availability of these MDR-TB treatments by filing for registration in more access countries, in particular the countries with a high burden of MDR-TB identified by the WHO, where it has commercialisation rights. Accessibility can be improved through public/private partnerships, patient assistance programmes and donations.

Expand registration of generic antibacterial and antifungal medicines. Viatris can expand registration of its generic antibiotics and antifungals listed on the 2021 WHO EML, such as linezolid, polymyxin B, and amphotericin b, to more countries, including low-income countries.

Fully decouple incentives for sales agents from sales volumes. Viatris does not promote pretomanid (Dovprela) and flucytosine. Viatris can expand this practice to all antibacterial and antifungal medicines. Alternatively, it can fully decouple incentives for sales agents from sales volumes of all antibacterial and antifungal medicines.

Adapt brochures and packaging. In order to support the appropriate use of its antibacterial and/or antifungal medicines by patients, Viatris can adapts its brochures and packaging to consider local languages, literacy levels, paediatric use, environmental conditions and patient adherence to treatment.

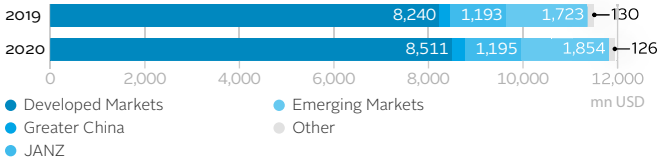
CHANGES SINCE 2020

Viatris was formed on November 16, 2020 through the combination of Mylan and Upjohn, a legacy division of Pfizer.

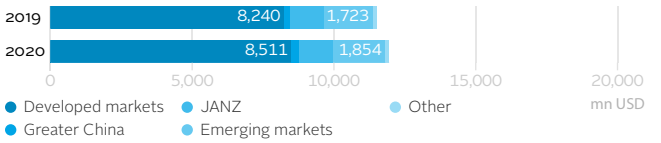
SALES AND OPERATIONS

Therapeutic areas: Cardiovascular, CNS and anesthesia, Dermatology, Diabetes and metabolism, Gastroenterology, Immunology, Infectious disease, Oncology, Respiratory and allergy, Women's healthcare.
Business segments: Developed Markets, Greater China, JANZ, Emerging markets
Product categories: Biosimilars, Generic medicines, Innovative medicines
M&A since 2020: Viatris was formed on November 16, 2020 through the combination of Mylan and Upjohn, a legacy division of Pfizer.

Revenue by business segment



Revenue by region



PORTFOLIO *for pathogens in scope*

Comparatively large portfolio: At least 87 products: 72 antibacterial medicines; 15 antifungal medicines
On-patent medicines: 2 (delamanid, pretomanid)
Off-patent/generic medicines: 9 of 85 were selected for analysis* (amoxicillin [A], amoxicillin/clavulanic acid [A], amphotericin b [F], flucytosine [F], isoniazid [T], linezolid [T], piperacillin/tazobactam [W], polymyxin B [R], vancomycin [W])
AWaRe medicines:** 24 Access group; 34 Watch group; 1 Reserve group
Anti-TB medicines:** 5

Products on the market

PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT

As a generic medicine manufacturer, Viatris is not evaluated in this Research Area.

B RESPONSIBLE MANUFACTURING Evaluated: antibacterials manufacturing (APIs and drug products)

B.1 Environmental risk-management for own sites and suppliers; tracks compliance with limits at own sites

Viatris reports a strategy to minimise the environmental impact of wastewaters and solid waste from antibacterial manufacturing at its sites, including audits every five years. It reports setting discharge limits in the receiving environment for all antibacterials manufactured at its sites, based on PNECs to limit AMR, as recommended by the AMR Industry Alliance. Discharge levels are quantified at all sites using a mass balance approach. All its sites, or 100%, are reported to be compliant with discharge limits. It reports that eight of its sites that manufacture antibacterials are ZLD and that recycled water was analysed for presence of antibacterials which was found to be zero.

Viatris requires third-party suppliers of antibacterials to follow the same standards, including limits based on PNECs. It engaged with EcoVadis to start an audit programme among its top 35 antibiotic suppliers to assess AMR risk. It also requests and reviews the discharge levels of its suppliers as part of these audits. It is unclear how many of the 35 suppliers are assessed so far and have quantified discharge levels.

There is limited information on the requirements Viatris makes of external private and public waste-treatment plants, in terms of strategy, audits and antibacterial discharge limits and levels.

B.2 Publicly discloses some information on environmental risk management and quantifying discharge levels at own sites

Viatris publishes some components of its environmental risk-management strategy. It is a member of the AMR Industry Alliance, which publishes a list of recommended antibacterial discharge targets. Viatris publishes its commitment to setting these targets. It also publicly discloses that all of its own sites have quantified antibacterial discharge levels. It does not publish: (1) the results of environmental audits, whether conducted at its own sites, the sites of suppliers or external private and public waste-treatment plants; (2) a list of these suppliers and plants; or (3) the levels of antibacterial discharge from its own or suppliers' sites.

B.3 System in place to maintain production quality for own and suppliers' sites; no requests for official corrective action

Viatris reports that its own sites and suppliers have a system to maintain high-quality antibacterial production consistent with international GMP standards. This includes periodic risk-based audits and tracking of corrective and preventive actions. Viatris also requires its suppliers to audit their own suppliers. The Benchmark found no requests for official corrective action from the FDA or EMA related to non-conformities with cGMP at Viatris' own sites or any subsidiaries that manufacture antibacterials.

* See Appendix VII for information about eligibility criteria for products.
** Listed on the 2019 WHO EML.

C APPROPRIATE ACCESS & STEWARDSHIP – ACCESS

Evaluated: access activities relating to antibacterial & antifungal medicines & vaccines in 102 access countries***

Viatris is not eligible for indicators: C.1.3 and C.2.3. For more information, see Appendix VII.

C.1.1 Filed to register on-patent medicines in 15 access countries on average

Viatris performs above average, filing its two relevant on-patent medicines for registration in access countries. Its most widely filed relevant product is the anti-tuberculosis medicine pretomanid, filed in 23 access countries, including five LICs. Under its licensing agreement with Otsuka, Viatris filed delamanid for registration in seven access countries.

C.1.2 Filed to register off-patent/generic medicines in 7 access countries on average

Viatris has an average performance, filing seven of its nine sample off-patent/generic medicines for registration in seven access countries on average. Its most widely filed relevant product is vancomycin, filed in 15 access countries. Six of its sample products are filed in less than 10 access countries. Five of its sample products are filed for registration in at least one LIC.

C.2.1 Several strategies to expand access to on-patent medicines

Viatris performs above average, with access strategies reported for both its two relevant on-patent medicines. It aims to expand access to its on-patent medicines in access countries through public/private partnerships, donations, tenders and a named patient access programme. Viatris partners with the GDF–Stop TB Partnership to provide pretomanid at a global access price of USD 364 per treatment course to 150 countries. Viatris provides evidence of patient reach and geographic reach for all its reported approaches. In 2019 and 2020, it provided 6,000 treatment courses of delamanid through a government tender in South Africa.

C.2.2 Some strategies to expand access to off-patent/generic medicines

Viatris has an average performance. It reports that it aims to expand access to its off-patent/generic medicines in access countries through equitable pricing and public/private partnerships. For example, Viatris partnered with stakeholders such as UNITAID, CHAI, and the Global Fund to provide flucytosine, prior to WHO-prequalification.

C.3 Several strategies to ensure continuous supply

Viatris performs above average, with strategies reported in all four areas assessed. Viatris ensures accurate demand planning and data sharing by having a 24-months horizon planning and daily, weekly, or monthly operational meetings and supply reviews. Viatris mitigates against shortage risks by keeping buffer stocks and conducting supplier audits. It registers several of its products at multiple production sites, including in China, South Africa, and Zambia, ensuring geographical diversification and dual sourcing. Viatris estimates 50% of its main products' APIs or finished forms to be dually sourced. To mitigate against sub-standard and falsified products, Viatris has a dedicated infrastructure to monitor product safety and manage related efforts. This includes, but is not restricted to, a product portfolio risk assessment process, analysis and market monitoring, a suspicious order monitoring programme, and a product diversion programme that includes anonymous reporting mechanisms and a supplier code of conduct. Viatris uses security features such as serialisation or 2D data matrix.

C APPROPRIATE ACCESS & STEWARDSHIP – STEWARDSHIP

Evaluated: stewardship activities relating to antibacterial & antifungal medicines globally

C.4 Comprehensive COI mitigation strategies in place for its educational programmes

Viatris performs strongly in conflict of interest (COI) mitigation for the five AMR-related educational programmes for HCPs assessed by the Benchmark. To mitigate COI for one programme, it provides financial resources to an independent third party (Omnicuris), which collaborated with another independent organisation (ISCCM) to develop the programme. The remaining four programmes have all three COI mitigation strategies looked for by the Benchmark: (1) content is developed independently from its marketing department; (2) a pledge not to provide financial or material incentives; and (3) it does not use branded materials.

C.5 Engages in sales practices but does not engage in marketing practices to address appropriate use

Viatris performs above average in sales practices. It does not deploy any sales agents to promote pretomanid and flucytosine to healthcare professionals. However, for the remaining antibacterial and/or antifungal medicines it does not report whether it decouples incentives for sales agents from sales volumes to help prevent the inappropriate use of such medicines.

Viatris does not report to engage in marketing practices that aim to address the appropriate use of its antibacterial and/or antifungal medicines as its marketing materials do not reflect emerging resistance trends or include treatment guidelines for healthcare professionals to raise awareness of AMR and address appropriate use.

C.6 Does not report adapting brochures and/or packaging to facilitate appropriate use by patients

Viatris does not report adapting brochures and/or packaging to facilitate the appropriate use of its antibacterial and/or antifungal medicines by patients.

C.7 AMR Surveillance

As a generic medicine manufacturer, Viatris is not assessed in this indicator but its activities in AMR surveillance are reported. The Benchmark notes that Viatris is active in two AMR surveillance programmes. It supports the national Data Development programme, which is a retrospective study of antimicrobial resistance in ICU patients in India and has been running since 2019. Viatris reports that it intends to share results in a peer-reviewed medical journal. Moreover, Viatris runs the multinational Pretomanid Resistance Surveillance Program, which is focused on resistance against pretomanid in eight countries until 2025. Once data collection has been completed, Viatris intends to share data with regulatory authorities and in a peer-reviewed journal article.

*** 102 low- and middle-income countries where better access to medicine is most needed.

Appendices

APPENDIX I

Analysis, scoring and review process

PROCESS FOR ANTIMICROBIAL PORTFOLIO ANALYSIS

The product portfolio database, including medicines and vaccines, was constructed using information from various sources, including proprietary data from IQVIA, public sources from pharmaceutical companies and supplemented (where relevant) with data from company submissions. The Benchmark requested the companies in scope to review, verify and provide additional data on their antibacterial and antifungal portfolio for analysis. Companies were asked to list each of their antibacterial or antifungal products' International Nonproprietary Name (INN) and brand name(s).

All products on the market as of 30 April 2021 (when the data collection period ended) were eligible for inclusion in the descriptive analysis of the product portfolio. The research team verified whether R&D projects included for analysis in the R&D Research Area were approved between the date of submission and until 30 April 2021. If approved between those dates, the product was included in the company's pipeline. R&D projects with market approval dates after the end of the period of analysis on 30 April 2021 and until 24 September 2021 (the time period during which the status of R&D projects was monitored by the Benchmark) were not added to the company's marketed product portfolio. In some instances, companies did not submit their entire antibacterial and antifungal portfolio during the data collection period. Products not submitted may include products with different INNs as well as products with the same INN but marketed under different brand names (e.g. in different countries/regions). For companies that did not participate in the Benchmark's survey, the initially pre-populated database was used for all descriptive product portfolio analyses.

To ensure products were within scope and eligible for analysis – i.e. antibacterial and antifungal medicines and vaccines for human use, both systemic and topical– and that there were no duplicate products within a company's submission, the research team reviewed and validated companies' submitted portfolios. For analyses at the individual company level, product data was aggregated at the INN level, since these were used to showcase the different active antibacterial and antifungal ingredients that the company marketed (formulations, doses, routes of administration or brand names were not differentiated). INN-level aggregation was performed both in the case of products with a single INN and fixed-dose combinations (FDCs) composed of two or more single-INN elements – therefore, two FDCs containing, e.g., the same single-INN components but with different doses in one or more of the components, were considered equivalent and aggregated. The Benchmark also considered that different salts of the same single-INN product or FDC component were considered equivalent and aggregated. On the other hand, product modifications that resulted in significantly different chemical/pharmaceutical properties were considered non-equivalent to the original product (examples include benzathine benzylpenicillin, a type of benzylpenicillin). The Benchmark also considered that combination products differing only in components that are not antimicrobials were equivalent and hence aggregated. Lastly, co-packaging of two products already marketed by a company (single-INN or FDC) did not count as an additional product. For the analysis combining companies' portfolios (in the portfolio analysis section of this report) no further data aggregation took place, meaning a product with a given INN, marketed by more than one company, was counted as many times as the number of companies that market it. The purpose of this was to provide an overview of the antibacterial and antifungal market.

Information regarding whether or not the product was listed on the WHO Model List of Essential Medicines (EML) was also verified by the research team. This final product portfolio, including 1521 products, was compared to the 21st WHO EML, published in 2019, to assess the number of products on this list. For a product to be considered by the Benchmark as a part of the EML, the INN, the specific formulation and strength had to be listed on the EML (chapter 6 anti-infectives and chapter 19.3 vaccines). Antibacterial medicines on the EML were further grouped according to the Access, Watch and Reserve (AWaRe) classification. Antituberculosis medicines were classified as: antituberculosis medicines. Products that could be linked to an EML product via a Square box were treated the same way as products that were mentioned on the EML and all alternatives listed were also included in the product portfolio database.

SUMMARY OF THE SCORING PROCESS

Companies were assessed and scored by the Benchmark in three Research Areas: Research & Development, Responsible Manufacturing and Appropriate Access and Stewardship, with each area composed of several indicators. Due to the variation between companies in scope, not all indicators were applicable to every company, as shown in the Indicators and Scoring Eligibility table in this Appendix.

The Benchmark included ongoing/active projects up until 30 April 2021 (when the data collection period ended), with two exceptions: (1) for R&D indicators, the status of R&D projects was monitored between 30 April 2021 and 24 September 2021 and R&D products approved up to 24 September 2021 were included as approved products in the report cards. Of note, (1) no additional R&D projects or changes of phase happening after 30 April 2021 were accounted for in the analysis; (2) for stewardship indicators, such as C.4 and C.7, programmes active at some point during the period of analysis were included, regardless of their ending date. Financial data from fiscal years 2019 and 2020 was used for analysis (the exact date marking the fiscal year end varies among companies).

Data review

Companies were asked to verify the accuracy of publicly sourced data and to provide additional necessary information. Prior to analysis, the Benchmark team reviewed companies' submissions for each of the Research Areas:

Research & Development: R&D projects consisting of antibacterial and antifungal medicines and vaccines were included for the overall pipeline. R&D projects eligible for scoring had to target at least one of the pre-defined priority pathogens (see Appendix V). R&D projects were classified as innovative or adapted. Adapted R&D projects do not involve a new chemical or biological entity (NCE or NBE); innovative R&D projects involve either an NCE or NBE. New medicines in clinical development were further classified as novel when they fulfilled one or more of the following criteria, defined by WHO in its 2020 analysis of the antibacterial clinical and preclinical development pipeline[1]: (a) it represents a new chemical class; (b) it aims at a new target; (c) it has a new mode of action; (d) it displays no cross-resistance with existing antimicrobials. After final submission and any necessary clarifications with the companies, all R&D projects were evaluated according to a standardised procedure.

Responsible Manufacturing: the Benchmark requested companies to share their policies on the manufacturing of antibacterial APIs and drug products. Information on environmental risk management was requested for company's own sites, suppliers' sites and external private and public waste treatment plants. The Benchmark further requested whether any of the sites or plants set limits on antibacterial discharge and quantified the discharge levels to determine compliance with limits. The qual-

ity of manufacturing was evaluated for not just drug products but also APIs at the sites of the company's own and suppliers' sites. Any GMP non-conformities at manufacturing sites were identified by reviewing public databases of the FDA and EMA. For transparency indicator B.2, the research team reviewed companies' public information on, e.g., corporate websites, annual reports and corporate social responsibility reports.

Appropriate Access: the Benchmark requested companies to share their access and stewardship policies for antibacterials and antifungals for the Research Area on Access, specifically the indicators Registration (C.1.1, C.1.2, C.1.3) and Expanding Access (C.2.1, C.2.2., C.2.3.). The Benchmark examined on- and off-patent medicines and vaccines separately. The on-patent antibacterial and antifungal medicines and vaccines were derived from the product portfolio as described above and were verified by the companies The selection of off-patent products (antibacterial and antifungal medicines) was based on each company's two highest volume sales data globally and in 21 low-income markets, which were provided by IQVIA Midas® based on sales data from 2017. These products were derived from the 2019 EML and were divided into six categories. Three categories were based on the 2019 WHO AWaRe Classification of Access, Watch, and Reserve and two categories were for Antifungal and Anti-Tuberculosis medicines. Companies' policies and strategies for these on- and off patent medicines and vaccines were then analysed in the various access-related indicators.

Stewardship: up to five: (a) educational stewardship activities; (b) AMR surveillance programmes; and (c) stewardship-oriented adaptations for patients were evaluated by the Benchmark for each company. In addition, the Benchmark evaluated sales and marketing practices that aim to address the appropriate use of the company's antibacterial and antifungal medicines. Finally, the Benchmark collected data around general AMR education for patients and the sharing of consumption data with public health authorities for reporting purposes.

Scoring

All indicators were scored from zero to five and weighted equally. When scoring a company on a quantitative indicator, such as financial investments or R&D pipeline size, the corresponding number was first scaled across all companies in scope for scoring.

When a given indicator was not applicable to a company, the company's maximum attainable score in the corresponding Research Area was decreased by an amount equal to the number of maximum points attainable in that indicator.

Scoring was carried out based on data from a wide range of information sources including company verification, independent reports and databases or documents from WHO, other multilateral organisations and Non-Governmental Organisations. For currency conversion to USD, exchange rates on the website x-rates.com were used.

Final scoring of the companies was the result of a multi-tiered analysis and quality assurance process. The quality assurance process included both systematic verification of scoring consistency and spot-checking. For each indicator, preliminary scoring results were used to make adjustments in scoring guidelines to ensure maximum variability of final results.

Review process

Following clarification and cross-check of company scores, the research team wrote the various sections of the Benchmark report. Each Research Area was reviewed by at least one externally appointed expert advisors. In addition to this, an external editorial review of the Benchmark report was performed.

METHODOLOGY DEVELOPMENT

To develop the methodology for the 2021 Antimicrobial Resistance Benchmark, the Foundation applied its proven process for building consensus on the role of pharmaceutical companies in tackling global health priorities. Strategic guidance was provided by an Expert Committee for the Benchmark, an independent body of experts, from top-level academic centres, donor governments, local governments in low- and middle-income countries, investors, and companies. The Expert Committee met in July 2020 to review proposals for the scope, structure, and analytical approach of the Benchmark. Their recommendations helped identify ways forward where disagreement or uncertainty existed regarding areas of research.

The Expert Committee members

Hans Hogerzeil (Chair)
Gregory Frank
Sudarshan Jain
Joakim Larsson
Marc Mendelson
Mirfin Mpundu
Maria Larsson Ortino
Sarah Paulin (Observer)

Stakeholders by group

Discussions were held with representatives of a wide range of organisations, a list of which can be found in the methodology report for the 2021 Antimicrobial Resistance Benchmark, available for download at www.amrbenchmark.org.

1. WHO. (2021). 2020 antibacterial agents in clinical and preclinical development: an overview and analysis. Retrieved from: https://www.who.int/publications/i/item/9789240021303

INDICATORS AND SCORING ELIGIBILITY

	IN SCOPE FOR R&D						FOR RM			IN SCOPE FOR AA							FOR STW			
	A1	A2.1	A2.2	A2.3	A2.4	A3	B1	B2	B3	C1.1	C1.2	C1.3	C2.1	C2.2	C2.3	C3	C4	C5	C6	C7
Large R&D-based pharmaceutical companies																				
GSK	●	●	●	●	●	●	●	●	●		●	●		●	●	●	●	●	●	●
Johnson & Johnson	●	●	●	●	●	●	●	●	●	●	●		●	●		●	●	●	●	●
MSD	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Novartis	●	●			●		●	●	●		●			●		●	●	●	●	●
Otsuka	●	●	●		●	●	●	●	●	●			●			●	●	●	●	●
Pfizer	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Sanofi	●	●	●	●	●	●	●	●	●		●	●		●	●	●	●	●	●	●
Shionogi	●	●	●	●	●	●	●	●	●	●	●		●	●		●	●	●	●	●
Generic medicine manufacturers																				
Abbott							●	●	●		●			●		●	●	●	●	
Alkem							●	●	●		●			●		●		●	●	
Aurobindo							●	●	●		●			●		●	●	●	●	
Cipla							●	●	●	●	●		●	●		●	●	●	●	
Fresenius Kabi							●	●	●		●			●		●	●	●		
Hainan Hailing							●	●	●		●			●		●		●	●	
Sun Pharma							●	●	●		●			●		●	●	●	●	
Teva							●	●	●		●			●		●		●	●	
Viatris							●	●	●	●	●		●	●		●	●	●	●	

Large research-based pharmaceutical companies were eligible for scoring in every research area, with a few exceptions. Generic medicine manufacturers were eligible for scoring in the RM, AA and STW research areas but not in R&D, as their main focus is the manufacturing of generic products. Large research-based pharmaceutical companies and generic medicines manufacturers were eligible to specific Appropriate Access indicators based on the products in their respective portfolio: all companies supplying on-patent antibacterial and antifungal medicines were eligible for indicators C.1.1 and C.2.1. All companies supplying off-patent/generic medicines were eligible for indicators C.1.2 and C.2.2. All companies supplying on-patent antibacterial and antifungal vaccines were eligible for indicators C.1.3 and C.2.3. In line with the external stakeholder consensus defined by the Foundation, generic medicine manufacturers were not eligible for scoring in indicator C.7 AMR Surveillance as they have thus far had a limited role in such activities.

APPENDIX II

Limitations

In this section we cover the main limitations faced in the Benchmark. All limitations, methodological, process or otherwise will be reviewed by the Foundation when undertaking future Benchmarks.

GENERAL METHODOLOGICAL LIMITATIONS

As in any survey, main limitations relate to coverage, sampling, non-responder and measurement biases. To the extent possible, the Benchmark research team worked to minimise the impact of these biases in the final results. On coverage and representativeness, we attempted to ensure that coverage of our survey represented as much as possible the wider antimicrobial industry players with relevant activities across the three Research Areas. The criteria used to select companies for the Benchmark is outlined in detail in our Methodology Report 2020. Companies are sometimes unwilling or unable to disclose data, or, if they do, may do so only partially. For example, the content of R&D projects and pricing information may be treated more cautiously by companies.

APPLICABILITY OF FINDINGS

Disease and product scopes

The outputs analysed in this study and the The outputs analysed in this study and the findings generated from it relate only to the disease and product scopes as outlined in the Antimicrobial Resistance Benchmark Methodology 2020. The 2021 Benchmark will focus on bacterial and fungal infections, particularly those identified as particular threats due to resistance, called priority pathogens, as determined by WHO and the CDC for the R&D research area. For the Responsible Manufacturing research area, the focus through stakeholder and expert review committee consensus was to focus on company's initiatives and activities around antibacterial APIs and drug products. The Appropriate Access research area assessed included companies' antibacterial and antifungal medicines and vaccines. The Stewardship research area assessed antibacterial and antifungal medicines.

Company comparability

Among the large research-based pharmaceutical companies and generic medicine manufacturers, companies were selected based on their antibacterial sales volume or value of their sales. Large research-based pharmaceutical companies were also selected for their antibacterial pipelines that have at least one antibacterial medicine or vaccine candidate targeting a priority pathogen in phase II or more advanced of clinical development and with an anti-infective product portfolio. Generic medicine manufacturers were also selected based on whether they are a large vendor of active pharmaceutical ingredients (APIs). The Benchmark findings on this category of companies should therefore be taken in this context.

Depending on the research area being analysed, different company types might be included in the analysis. For instance, within the R&D research area, indicators on the pipeline are applicable to large research-based pharmaceutical companies but not to generic medicine manufacturers. Both company types are quite different with vastly different business models. In the Benchmark analysis, we adjusted for these variations between company types, company size, and company portfolio whenever relevant and possible. Further, the Benchmark provides key information about companies' antibacterial and antifungal business in several sections of the report, which readers should take into account as important context when interpreting the Benchmark findings.

Different factors may affect companies' capacity for reporting information. Some companies have submitted only a selection of their antibacterial and antifungal business to the Benchmark. Hence, the data presented in the "Portfolio Analysis" section of this report and on individual company report cards may not necessarily represent their entire portfolio resulting in a potential underreporting of the number of essential medicines on the 2019 WHO EML. Different companies also use different nomenclature and have different ways of categorising information. For example, when calculating the value of antibacterial and antifungal R&D investments or revenue from antibacterial and antifungal sales, such disaggregated data might not be readily available. In an effort to minimise variability in interpretation and ensure data consistency, a glossary of definitions was published in the Benchmark Methodology Report 2020.

Data Availability

As in all survey methodologies, the data of the Benchmark is dependent on company submissions as the source data as well as on data available in the public domain. To mitigate any reporting bias and for scoring purposes, every effort was made to triangulate company-submitted data by verifying it against public sources, such as company annual reports, WHO reports, and clinical trial registries. Insofar triangulation was not possible, data submitted by the companies was used for scoring. For example, in the R&D research area, while clinical stage projects could be verified with publicly available data, information on discovery and preclinical stage projects was often obtained from company submissions. Both sets of information were used for analysis and scoring. Hence, the comprehensiveness and level of detail available in public sources and in the data submitted by the companies are thus limiting factors in the Benchmark analysis. Furthermore, some information was submitted by companies on the basis of confidentiality, thus making the Benchmark's ability to analyse and report conclusions across several indicators challenging.

APPENDIX III

Scoring guidelines

A RESEARCH & DEVELOPMENT

A.1 R&D INVESTMENTS

R&D investments (including in-kind) dedicated to the development of antibacterial and antifungal medicines and vaccines targeting pathogens in scope during fiscal years 2019 and 2020.

3-5 The percentage of the company's revenue derived from pharmaceuticals (and vaccines if active in vaccine development) that it then invests (spends) in the development of antibacterial and/or antifungal medicines and/or vaccines targeting pathogens in scope.
This number is scaled across all companies that disclose their investments.

2 The company invests in R&D and it does not disclose. The company also pledges funds to the AMR Action Fund or it supports AMR R&D indirectly with considerable funds.

1 The company does not invest in-house in R&D AMR projects, but it pledges funds to the AMR Action Fund or it supports AMR R&D indirectly with considerable funds.

0 The company does not invest in the development of antibacterial and antifungal medicines and vaccines for medicines in scope directly or indirectly.

N/A Generic medicine manufacturers are not scored in this indicator.

A.2.1 PIPELINE SIZE

The size of a company's R&D pipeline targeting priority pathogens, including antibacterial and antifungal medicines and vaccines (new chemical/biological entities and adaptations) developed in-house or through collaborations.

1-5 The sum of medicines and vaccines projects in development, or having received approval during the period of analysis, that target pathogens in scope.
This number is scaled across all companies and scored.

0 The company has no relevant R&D activity within the scope of this indicator.

N/A Generic medicine manufacturers are not scored in this indicator.

A.2.2 NOVELTY OF PIPELINE

The novelty of new investigational clinical antibacterial and antifungal medicines targeting priority pathogens that the company is developing (in-house or through collaborations). A new product candidate in development is defined as containing at least one new component (entity) not previously approved.

5 The company has more than 1 innovative medicine project in clinical development described in the WHO's 'Antibacterial agents in clinical and preclinical development' as fulfilling any of the innovativeness criteria.

4 The company has at least 1 innovative medicine project in clinical development described in the WHO's 'Antibacterial agents in clinical and preclinical development' as fulfilling any of the innovativeness criteria. Criteria is extended to antifungals.

3 The company has more than one innovative medicine project in clinical development.

2 The company has at least 1 innovative medicine project in clinical development.

1 The company has only adaptive projects in clinical development.

N/A The company does not have any medicine project in clinical development.
Generic medicine manufacturers are not scored in this indicator.

A.2.3 VACCINES IN THE PIPELINE

The number of vaccines that the company is developing for priority pathogens in scope (in-house or through collaborations).

5 The company has a large vaccine pipeline, ($n \geq 10$), mostly focused on new projects that contain at least one new biological component (entity) not previously approved.

4 The company has a medium-sized vaccine pipeline, ($n \geq 5$ to $n < 10$), mostly focused on new projects that contain at least one new biological component (entity) not previously approved.

3 The company has a small vaccine pipeline, ($n < 5$), and at least half (≥50%) of the pipeline is focused on new projects that contain at least one new biological component (entity) not previously approved.

2 The company has a small vaccine pipeline, ($n < 5$), and at least half (≥50%) of the pipeline is focused on adaptive projects (i.e. projects that do not include a new biological entity).

N/A The company is not engaged in vaccine development and therefore has no relevant R&D activity within the scope of this indicator.
Generic medicine manufacturers are not scored in this indicator.

A.2.4 PROJECTS TARGETING CRITICAL PRIORITIES

The number of projects that target a 'critical' pathogen (as defined by WHO) and/or 'urgent' pathogen (as defined by the CDC). These pathogens include carbapenem-resistant (CR) *Acinetobacter* spp., *C. auris*, *C. difficile*, CR or ESBL-producing *Enterobacteriaceae*, drug-resistant *N. gonorrhoeae* and CR *P. aeruginosa*.

5 The company has 8 or more projects with unique candidates/combinations targeting critical/urgent priorities.

4 The company between 4 and 7 projects with unique candidates/combinations targeting critical/urgent priorities.

3 The company has 3 projects with unique candidates/combinations targeting critical/urgent priorities.

2 The company has 2 projects with unique candidates/combinations targeting critical/urgent priorities.

1 The company has 1 project targeting critical/urgent priorities

0 The company does not have projects targeting critical/urgent priorities.

N/A Generic medicine manufacturers are not scored in this indicator.

A.3 ACCESS AND STEWARDSHIP PLANNING

The proportion of late-stage antibacterial and antifungal R&D projects targeting priority pathogens, for which the company provides information about having plans in place for 1) access in countries in scope and where burden of disease is higher; and 2) stewardship on a global scale. This indicator applies to late-stage R&D projects in Phase II and III of clinical development (developed in-house or through collaborations) and recently approved products.

5 The company has a large late-stage pipeline with comprehensive portfolio-wide policies and project-specific access and stewardship (as applicable) plans for all relevant projects. Plans include clear access-oriented policies across the company's portfolio with elements such as the intention to file for registration in 'access countries', ensuring the breadth of access components incorporate considerations for affordability and supply, engaging in surveillance, and using evidence from local patterns of disease and/or resistance to inform all activities.

4 "The company has comprehensive and project-specific access and stewardship (as applicable) plans for all late-stage medicines and vaccines.
OR
The company has a large late-stage pipeline with company-wide access and stewardship commitments and some project-specific plans that reflect the company's access-oriented intentions."

3 The company has project-specific access and stewardship (as applicable) plans in place for all of its late-stage projects.

2 The company has at least one late-stage project with a project-specific access (for medicines and vaccines) and/or stewardship (for medicines) plan.

1 The company has general commitments or policies in place to develop access and/or stewardship plans for late-stage R&D projects, but the company provides no clear evidence of such plans being applied to existing late-stage R&D candidates.

0 The company reports having neither access nor stewardship plans or commitments for its late-stage R&D candidates.

N/A The company does not have any late-stage projects and is therefore not in scope for this indicator. Generic medicine manufacturers are not scored in this indicator.

B RESPONSIBLE MANUFACTURING

B.1 ENVIRONMENTAL RISK-MANAGEMENT STRATEGY

The company has an environmental risk-management (ERM) strategy to minimise the environmental impact of manufacturing discharge of antibacterials that includes:
(i) implementation of waste-treatment practices for both liquid and solid antibacterial-containing wastes taking AMR risk into account
(ii) on-site auditing of compliance with the strategy
(iii) setting of antibacterial discharge limits based on predicted no-effect concentrations (PNECs) for resistance selection
(iv) monitoring/quantification of the levels of antibacterials discharged in wastewaters to assess and manage risk that limits are surpassed

The points above apply to the company's:
(a) owned and/or operated manufacturing sites
(b) third-party suppliers of antibacterial active pharmaceutical ingredients (APIs) and/or drug products
(c) external privately-owned* or public waste-treatment plants

Elements (i) to (iv) define the depth of the strategy and elements (a) to (c) define its breadth. There are a total of 12 elements, corresponding to the 12 combinations of 4 depth elements with 3 breadth elements. In the case of waste-treatment plants, depth elements (iii) and (iv) were merged for the scoring process, resulting in a maximum total of 11 elements assessed by the Benchmark. Each element was considered fully, partially or not met and assigned 1, 0.5 or 0 points, respectively. Points were summed to obtain the final score. Some elements were not applicable to all companies which was accounted for in final scoring.

5 The company demonstrates an ERM strategy that covers 8.5 or more of the applicable indicator elements.
4 The company demonstrates an ERM strategy that covers 7-8 of the applicable indicator elements.
3 The company demonstrates an ERM strategy that covers 5-6.5 of the applicable indicator elements.
2 The company demonstrates an ERM strategy that covers 3-4.5 of the applicable indicator elements.
1 The company demonstrates an ERM strategy that covers 0.5-2.5 of the applicable indicator elements.
0 The company demonstrates an ERM strategy that covers 0 of the applicable indicator elements.
** Off-site plants that are more than 50% owned by private parties, which may or may not include the company itself.*

B.2 DISCLOSURE ON ENVIRONMENTAL RISK MANAGEMENT

The company publishes the following elements:
(a) components of its ERM strategy to minimise environmental impact of wastewaters and solid waste from antibacterial manufacturing
(b) results of strategy audits at the company's manufacturing sites, third-party sites manufacturing antibacterial APIs and drug products and/or external private waste-treatment plants
(c) identities of third parties manufacturing antibacterial APIs and drug products and/or of external private waste-treatment plants
(d) levels (concentrations) of antibacterial discharge and discharge monitoring/quantification
(e) limits set for antibacterial discharge, along with methodological and evidential bases*.

5 The company publishes 5 of the 5 indicator elements.
4 The company publishes 4 of the 5 indicator elements.
3 The company publishes 3 of the 5 indicator elements.
2 The company publishes 2 of the 5 indicator elements.
1 The company publishes 1 of the 5 indicator elements.
0 The Benchmark found none of the indicator elements published in the company's website, annual report, or CSR/EHS reports.
** Discharge limits published on the AMR Industry Alliance website were also considered for this element in the 2021 Benchmark, despite not qualifying as disclosure via an official individual company source.*

B.3 MANUFACTURING HIGH-QUALITY ANTIBACTERIALS

The company makes commitments, has systems in place and promotes initiatives to ensure, maintain and/or improve the production of high-quality antibacterial APIs and drug products at its own and suppliers' manufacturing sites, in a manner consistent with the international standards developed and accepted by recognised national and international authorities.
To accomplish this, the company reports having a quality system that meets the following five elements:
(1) it is consistent with international standards such as FDA, EU and/or WHO Good Manufacturing Practice (GMP) at all own and/or suppliers' sites.
(2) it includes quality monitoring procedures at own and suppliers' sites, e.g. periodic auditing
(3) it includes a system for implementation and tracking of corrective and preventive actions at own and suppliers' sites
(4) it includes a requirement of its suppliers in scope to conduct periodic on-site audits of their own suppliers' sites
(5) the authorities above, as applicable, have not publicly reported GMP non-conformities at companies' own sites or sites of wholly-owned direct subsidiaries, during the period of analysis

Regarding the fourth element, after publication of the Methodology on 06 October 2020, this element was added to the scoring process to assure high-quality manufacturing deeper into the supply chain.

Regarding the fifth element, the Benchmark considered non-conformities* to be either (a) inspections with a result of 'Official Action Indicated' (OAI) as made publicly available in the FDA's Inspection Classification Database under the 'Drug Quality Assurance' project area, or (b) non-compliance reports found in the EMA EudraGMP database, both referring to inspections with end date within the period of analysis, 22 June 2019 to 30 April 2021, inclusive. Databases were last consulted on 22 October 2021.

5 The company reports having a quality system that meets 5 of the 5 indicator elements.
4 The company reports having a quality system that meets 4 of the 5 indicator elements.
3 The company reports having a quality system that meets 3 of the 5 indicator elements.
2 The company reports having a quality system that meets 2 of the 5 indicator elements.
1 The company reports having a quality system that meets 1 of the 5 indicator elements.
0 The company demonstrates no information on a quality system that meets any of the 5 indicator elements.
** It was sometimes not possible to determine whether the sites affected by non-conformities produced antibacterials. Such non-conformities were nevertheless taken into account in the Benchmark assessment, since they suggest potential risks regarding how the companies' reported quality system (usually covering all sites) is being implemented at sites producing antibacterials.*

C APPROPRIATE ACCESS

C.1.1 REGISTRATION OF ON-PATENT ANTIBACTERIAL AND ANTIFUNGAL MEDICINES

Companies are assessed according to the average number of access countries in which on-patent antibacterial and antifungal medicines have been filed for registration.

5 The company files its on-patent medicines for registration in >40 access countries on average.
4 The company files its on-patent medicines for registration in 11-40 access countries on average.
3 The company files its on-patent medicines for registration in 6-10 access countries on average.
2 The company files its on-patent medicines for registration in 1-5 access countries on average.
1 The company has on-patent medicines that have been filed in at least one access country, but files them in less than one access country on average or there is little information available.
0 The company has on-patent medicines, but there is no evidence of filing in access countries.

C.1.2 REGISTRATION OF OFF-PATENT/GENERIC ANTIBACTERIAL AND ANTIFUNGAL PRODUCTS

Companies are assessed according to the average number of access countries in which eligible off-patent/generic antibacterial, antifungal, and anti-tuberculosis medicines have been filed for registration.

5 The company files its eligible off-patent products for registration in >40 access countries on average.
4 The company files its eligible off-patent products for registration in 11-40 access countries on average.
3 The company files its eligible off-patent products for registration in 6-10 access countries on average.
2 The company files its eligible off-patent products for registration in 1-5 access countries on average.
1 The company has eligible off-patent products that have been filed in at least one access country, but files them in less than one access country on average or there is little information available.
0 The company has eligible off-patent products, but there is no evidence of filing in access countries.

C.1.3 REGISTRATION OF ON-PATENT ANTIBACTERIAL AND ANTIFUNGAL VACCINES

Companies are assessed according to the average number of access countries in which on-patent antibacterial and antifungal vaccines have been filed for registration.

5 The company files its on-patent vaccines for registration in >40 access countries on average.
4 The company files its on-patent vaccines for registration in 11-40 access countries on average.
3 The company files its on-patent vaccines for registration in 6-10 access countries on average.
2 The company files its on-patent vaccines for registration in 1-5 access countries on average.
1 The company has on-patent vaccines that have been filed in at least one access country, but files them in less than one access country on average or there is little information available.
0 The company has on-patent vaccines, but there is no evidence of filing in access countries.

C.2.1 EXPANDING ACCESS TO ON-PATENT ANTIBACTERIAL AND ANTIFUNGAL MEDICINES

Companies are assessed on the access strategies they use to expand access to and ensure affordability of their on-patent antibacterial and antifungal medicines in access countries. Each access strategy reported by a company is assessed against five main elements:
(a) Access strategy: the company reports a clear, well-described, and detailed access strategy, either at product level or on a wider scale.
(b) Pricing strategy: the company considers ability to pay when setting the price of its on-patent medicines and indicates what factors are taken into account to address ability to pay (e.g., socio-economic and/or demographic factors).
(c) Evidence of geographic reach: the company reports on the geographic scope of its access strategy.
(d) Evidence of patient reach: the company reports on the number of patients reached by its access strategy in access countries.
(e) Acknowledgment of access needs and commitment to expand access: the company acknowledges the access needs in access countries and demonstrates commitment to expand access to its on-patent medicines to more people in more countries.

1-5 Each of the five elements was assigned between 0 and 2 points.
The points were summed, and the total was brought to a score out of 5 to get the final score.
For example, the company received a maximum score of 5 if it met all the above elements: the company takes a proactive approach and demonstrates willingness to reach more people with its medicines in access countries, including those with a high disease burden. The company uses and combines a range of strategies. Access strategies are clear, well described, and detailed – specifying patient reach and geographic reach, and considering ability to pay where appropriate.
0 The company reports no evidence of providing access to its on-patent medicines in access countries.

C.2.2 EXPANDING ACCESS TO OFF-PATENT/GENERIC ANTIBACTERIAL AND ANTIFUNGAL PRODUCTS

Companies are assessed on the access strategies they use to expand access to their eligible off-patent/generic medicines in access countries. Each access strategy reported by a company is assessed against four main elements:
(a) Access strategy: the company reports a clear, well-described, and detailed access strategy, either at product level or on a wider scale.
(b) Evidence of geographic reach: the company reports on the geographic scope of its access strategy.
(c) Evidence of patient reach: the company reports on the number of patients reached by its access strategy in access countries.
(d) Acknowledgment of access needs and commitment to expand access: the company acknowledges the access needs in access countries and demonstrates commitment to expand access to its off-patent/generic medicines to more people in more countries.

1-5 Each of the five elements was assigned between 0 and 2 points. The points were summed, and the total was brought to a score out of 5 to get the final score.
For example, the company received a maximum score of 5 if it met all the above elements: the company takes a proactive approach and demonstrates willingness to reach more people with its medicines in access countries, including those with a high disease burden. The company uses and combines a range of strategies. Access strategies are clear, well described, and detailed – specifying patient reach and geographic reach.

0 The company reports no evidence of providing access to its off-patent/generic products in access countries.

C.2.3 EXPANDING ACCESS TO ON-PATENT ANTIBACTERIAL AND ANTIFUNGAL VACCINES

Companies are assessed on the access strategies they use to expand access to and ensure affordability of their on-patent antibacterial and antifungal vaccines in access countries. Each access strategy reported by a company is assessed against five main elements:
(a) Access strategy: the company reports a clear, well-described, and detailed access strategy, either at product level or on a wider scale.
(b) Pricing strategy: the company considers ability to pay when setting the price of its on-patent vaccines and indicates what factors are taken into account to address ability to pay (e.g., socio-economic and/or demographic factors).
(c) Evidence of geographic reach: the company reports on the geographic scope of its access strategy.
(d) Evidence of patient reach: the company reports on the number of patients reached by its access strategy in access countries.
(e) Acknowledgment of access needs and commitment to expand access: the company acknowledges the access needs in access countries and demonstrates commitment to expand access to its on-patent vaccines to more people in more countries.

1-5 Each of the five elements was assigned between 0 and 2 points. The points were summed, and the total was brought to a score out of 5 to get the final score.
For example, the company received the maximum score of 5 if it met all the above elements: the company takes a proactive approach and demonstrates willingness to reach more people with its medicines in access countries, including those with a high disease burden. The company uses and combines a range of strategies. Access strategies are clear, well described, and detailed – specifying patient reach and geographic reach, and considering ability to pay where appropriate.

0 The company reports no evidence of providing access to its on-patent vaccines in access countries.

C.3 ENSURING CONTINUOUS SUPPLY

Companies are assessed according to four main elements representing areas they can engage in to ensure the continuous supply of their products: demand planning and data sharing, shortage mitigation, capacity building and technology transfers and substandard and falsified medicines mitigation.
(a) Demand planning and data sharing: The company ensures accurate demand planning and data sharing, including the stakeholders and the frequency with which it informs them about its demand plans.
(b) Shortage mitigation strategies: The company employs strategies to mitigate shortage risks including whether there is a buffer stock; whether the company audits its stock; whether there is a dedicated task force to manage the supply chain and prevent shortages; and whether the company promotes API supplier diversity, including risk mitigation for APIs with single suppliers.
(c) Capacity Building and technology transfers: The company promotes capacity building and technology transfer initiatives for the manufacturing of antibacterial and antifungal products, mentioning where these initiatives are implemented and demonstrating how they strengthen supply chain in the access countries.
(d) Substandard and falsified medicines mitigation: The company employs strategies to mitigate the circulation of substandard and falsified medicines.

1-5 Each of the four elements was assigned between 0 and 7 points. The points were summed, and the total was brought to a score out of 5 to get the final score.

0 The company reports no evidence of ensuring the continuous supply of its medicines or vaccines in access countries.

C STEWARDSHIP

C.4 EDUCATIONAL STEWARDSHIP ACTIVITIES

The company has a clear strategy to ensure that any conflict of interest (COI) is mitigated in its (support of) antibacterial and antifungal stewardship educational activities directed at healthcare professionals. To mitigate COI, the company provides an unrestricted grant to an independent third party to develop the educational activity, or if it is developed in-house, the company ensures COI is mitigated through an independent review of the educational activity by a third party such as an accreditation body.

5 The company engages in AMR-related educational programmes aimed at healthcare professionals (HCPs) with comprehensive conflict of interest (COI) mitigation* for all of its programmes (up to five programmes total).

4 The company engages in AMR-related educational programmes aimed at HCPs with comprehensive COI mitigation* for the majority (more than half) of its programmes (up to five programmes total).

3 The company engages in AMR-related educational programmes aimed at HCPs with comprehensive COI mitigation* for the minority (less than half) of its programmes (up to five programmes total).
OR
The company engages in AMR-related educational programmes aimed at HCPs with some COI mitigation for its programmes (up to five programmes total). Some COI mitigation refers to including any of the three of the Benchmark's defined COI mitigation strategies.**

0 The company engages in AMR-related educational programmes aimed at HCPs without any COI mitigation.

N/A The company does not engage in AMR-related educational programmes aimed at HCPs and is therefore not eligible for assessment of COI mitigation for such programmes.

** Comprehensive COI mitigation can be done either by:*
(1) providing an unrestricted grant to an independent third party to develop the programme; or
(2) if developed in-house, ensuring an independent evaluation of the programme (e.g. by receiving accreditation or by a review committee);
or
*(3) implementing all three of the Benchmark's defined COI mitigation strategies.***
*** The three COI mitigation strategies are: (a) ensuring that the content and speaker selection is independent from the marketing department; (b) pledging not to provide financial or material incentives to participants; and (c) ensuring there are no branded products or materials in the content of the programme.*

C.5 RESPONSIBLE PROMOTIONAL PRACTICES

Responsible promotional practices when engaging with healthcare professionals include sales practices that aim to avoid overselling of antibacterials and antifungals by either not promoting such products or by decoupling incentives for sales agents from sales volumes. In addition, the company adapts its marketing materials to include AMR trends and guidelines for healthcare professionals.

5
- The company does not promote any of its antibacterial and/or antifungal medicines to healthcare professionals (e.g. by not deploying sales agents or by only participating in tenders for the sales of such medicines).
- The company fully decouples incentives for sales agents from sales volumes for all of its antibacterial and/or antifungal medicines AND reflects emerging resistance trends and/or treatment guidelines for healthcare professionals (HCPs) in its marketing materials. Full decoupling means there is no variable pay in sales agents' total pay linked to sales volumes.

4 The company reflects emerging resistance trends and/or treatment guidelines for HCPs in its marketing materials AND fulfils at least one of the following points:
- The company does not promote at least one antibacterial and/or antifungal medicine OR does not promote such medicines in some geographies to HCPs (e.g. by not deploying sales agents or by only participating in tenders for the sales of such medicines).
- The company fully decouples incentives for sales agents from sales volumes for at least one antibacterial and/or antifungal medicine OR fully decouples incentives for sales agents from sales volumes for such medicines in some geographies. Full decoupling means there is no variable pay in sales agents' total pay linked to sales volumes.
- The company partly decouples incentives for sales agents from sales volumes for 98% and for all of its antibacterial and/or antifungal medicines in all geographies. Partial decoupling means (part of) the variable pay in sales agents' total pay is based on sales volumes.

3 • The company reflects emerging resistance trends and/or treatment guidelines for HCPs in its marketing materials.
• The company does not promote at least one antibacterial and/or antifungal medicine OR does not promote such medicines in some geographies to HCPs (e.g. by not deploying sales agents or by only participating in tenders for the sales of such medicines).
• The company fully decouples incentives for sales agents from sales volumes for at least one antibacterial and/or antifungal medicine OR fully decouples incentives for sales agents from sales volumes for such medicines in some geographies. Full decoupling means there is no variable pay in sales agents' total pay linked to sales volumes.
• The company partly decouples incentives for sales agents from sales volumes for all of its antibacterial and/or antifungal medicines in all geographies. Partial decoupling means (part of) the variable pay in sales agents' total pay is based on sales volumes.

0 The company does not report engaging in practices that aim to address the appropriate use of its antibacterial and/or antifungal medicines, either regarding its sales practices or its marketing materials.

Bullet points refer to OR situations.

C.6 STEWARDSHIP-ORIENTED ADAPTATIONS FOR PATIENTS

The company adapts its brochures and/or its packaging to facilitate the appropriate use of antibacterial and antifungal products by patients. The company considers the needs of the patient population, including language, literacy, and paediatric use (if relevant). In addition, the company aims to improve adherence to treatment and considers local environmental conditions to preserve the effectiveness.

5 The company adapts its brochures and/or packaging to take account of all patient needs: language, literacy levels, paediatric use*, adherence to treatment and environmental conditions.

4 The company adapts its brochures and/or packaging to take account of at least two patient needs: language, literacy levels, paediatric use*, adherence to treatment and/or environmental conditions.

3 The company adapts its brochures and/or packaging to take account of only one patient need: language, literacy levels, paediatric use*, adherence to treatment or environmental conditions.

0 The company does not adapt its brochures and/or packaging to facilitate the appropriate use of its antibacterial and/or antifungal medicines by patients.

N/A The company only sells antibacterial and/or antifungal medicines that are administered by healthcare professionals rather than by patients and is therefore not eligible for assessment of adaptations to facilitate appropriate use by patients.

** Adaptations for paediatric use are only assessed if the company has any products in its portfolio for paediatric use.*

C.7 AMR SURVEILLANCE

The company has, supports, and/or contributes to antibacterial and antifungal surveillance programmes to track resistance to pathogens, and shares such data publicly.

5 The company publicly shares* raw data of at least one AMR surveillance programme.

4 The company shares raw data of at least one AMR surveillance programme on a data platform in a restricted manner.

3 The company publicly shares* aggregated results of at least one AMR surveillance programme.

2 The company does not publicly share* raw data or aggregated results of its AMR surveillance programme(s).

0 The company does not report any involvement in AMR surveillance programmes.

N/A The company is involved in AMR surveillance programme(s) but its data collection is not yet completed and is therefore not eligible for data sharing.
Generic medicine manufacturers are not assessed in this indicator as they have a limited role in AMR surveillance activities.

** Publicly sharing surveillance data can be done through open-access data platforms or peer-reviewed open-access journal articles.*

APPENDIX IV

Identifying best practices

The diffusion of best practices is one of the Benchmark's mechanisms for supporting the pharmaceutical industry in curbing AMR. Recognising those companies piloting or scaling up unique industry policies or initiatives is an important way of acknowledging those companies prepared to stand out from peers.

BEST PRACTICES

Best practices are ones that can be accepted as being the most effective way of achieving a desired end, relative to what the industry is currently doing in that area and what stakeholder expectations are. It can also be described as a benchmark. Best practices are not new practices – they have already been conceived of, applied and proven to meet at least some of the following criteria:

- Sustainability;
- Replicability;
- Alignment with external standards/stakeholder expectations;
- Proven effectiveness.

In different areas of analysis (for example, in Research & Development vs. in Appropriate Access) how a best practice is identified may be different. A best practice need not be unique amongst companies. A best practice might be an example of a 'gold standard' of practice; a best-in-class policy; or a strategy, programme, product initiative or group of behaviours closely aligned with stakeholder expectations. Best practices should be considered as the exemplar of positive practices in the corresponding research area in comparison to those of the other companies that submitted data within the current period of analysis. These best practices are identified based on evidence of progress submitted in the data collection period and verified with public information and through consultation with experts, where appropriate.

PROCESS

To determine which of the company's practices would be highlighted as best practice, the Foundation's research team evaluated all aspects of company practices, compiling those that met the criteria used for the purpose of scoring with additional standards for each Research Area, where necessary. Practices that met these outlined criteria were reviewed and finalised by the Foundation's senior management with additional input from experts in the corresponding field, when required.

APPENDIX V

Priority pathogens included for analysis in R&D

In the Research & Development Research Area, the Benchmark will assess the size and public health value of a company's pipeline of investigational antibacterial and antifungal medicines and vaccines. The disease scope for the 2021 AMR Benchmark includes the pathogens, with their specific resistance profiles, from the priority pathogens lists published by World Health Organization (WHO)[1] and the Centers for Disease Control and Prevention (CDC)[2] (see full list below).

Indicator A.2.4 of the Benchmark will assess companies' projects targeting the most critical priorities in these lists, i.e. targeting the pathogens classified by the CDC and WHO as "Urgent" or "Critical", respectively.

Pathogen	WHO Priority List[1]	Resistance profile	CDC Biggest Threats[2]	Resistance profile
BACTERIA				
Acinetobacter spp.	Critical	Carbapenem	Urgent	Carbapenem
Bordetella pertussis			Watch	Drug-resistant
Campylobacter spp.	High	Fluoroquinolones	Serious	Drug-resistant
Clostridioides difficile			Urgent	
*Enterobacteriaceae**	Critical	Carbapenem Extended-Spectrum ß-Lactamase (ESBL)	Urgent Serious	Carbapenem Extended-Spectrum ß-Lactamase (ESBL)
Enterococcus faecium	High	Vancomycin (VRE)		
Enterococcus spp.			Serious	Vancomycin (VRE)
Haemophilius influenzae type b (Hib)	Medium	Ampicillin		
Helicobacter pylori	High	Clarithromycin		
Mycobacterium tuberculosis	R&D priority		Serious	Drug-resistant
Mycoplasma genitalium			Watch	Drug-resistant
Neisseria gonorrhoeae	High	Cephalosporins Fluoroquinolones	Urgent	Drug-resistant
Pseudomonas aeruginosa	Critical	Carbapenem	Serious	Multidrug-resistant (MDR)
Salmonella spp.	High	Fluoroquinolones		
Salmonella non-typhoidal & serotype typhi			Serious	Drug-resistant
Shigella spp.	Medium	Fluoroquinolones	Serious	Drug-resistant
Staphylococcus aureus	High	Methicillin Vancomycin-intermediate and resistant	Serious	Methicillin (MRSA)
Streptococcus (group A)			Concerning	Erythromycin
Streptococcus (group B)			Concerning	Clindamycin
Streptococcus pneumoniae	Medium	Penicillin-non-susceptible	Serious	Drug-resistant
FUNGI				
Aspergillus fumigatus			Watch	Azole-resistant
Candida auris			Urgent	
Candida spp.			Serious	Drug-resistant

* *Enterobacteriaceae* has been renamed to Enterobacterales.

REFERENCES

1 WHO. (2017). Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics.
2 U.S. Centers for Disease Control and Prevention (CDC). (December 2019). Antibiotic resistance threats in the United States, 2019.

APPENDIX VI

Access countries

List of countries covered by access metrics for the 2021 Antimicrobial Resistance Benchmark – 102 countries

EAST ASIA & PACIFIC	
Cambodia	LMIC
China	HIDBC
Indonesia	LMIC
Kiribati	LMIC
Korea, Dem. People's Rep.	LIC
Lao PDR	LMIC
Micronesia, Fed. Sts.	LMIC
Mongolia	LMIC
Myanmar	LMIC
Papua New Guinea	LMIC
Philippines	LMIC
Solomon Islands	LMIC
Thailand	HIDBC
Timor-Leste	LMIC
Tuvalu	LDC
Vanuatu	LMIC
Vietnam	LMIC
EUROPE & CENTRAL ASIA	
Georgia	LMIC
Kosovo	LMIC
Kyrgyz Republic	LMIC
Moldova	LMIC
Tajikistan	LIC
Turkmenistan	HIHDC
Ukraine	LMIC
Uzbekistan	LMIC
LATIN AMERICA & CARIBBEAN	
Belize	HIHDC
Bolivia, Plurinat. State	LMIC
Brazil	HIHDC
Colombia	HIHDC
Dominican Republic	HIHDC
El Salvador	LMIC
Guatemala	MHDC
Guyana	MHDC
Haiti	LIC
Honduras	LMIC
Mexico	HIDBC
Nicaragua	LMIC
Paraguay	HIHDC
Peru	HIDBC
Suriname	HIHDC
MIDDLE EAST & NORTH AFRICA	
Djibouti	LMIC
Egypt, Arab Rep.	LMIC
Iraq	MHDC
Morocco	LMIC
Syrian Arab Republic	LIC
Tunisia	LMIC
Palestine, State / West Bank and Gaza	LMIC
Yemen, Rep.	LIC
SOUTH ASIA	
Afghanistan	LIC
Bangladesh	LMIC
Bhutan	LMIC
India	LMIC
Maldives	HIHDC
Nepal	LIC
Pakistan	LMIC
Sri Lanka	LMIC
SUB-SAHARAN AFRICA	
Angola	LMIC
Benin	LIC
Botswana	HIHDC
Burkina Faso	LIC
Burundi	LIC
Cabo Verde	LMIC
Cameroon	LMIC
Central African Republic	LIC
Chad	LIC
Comoros	LIC
Congo, Dem. Rep.	LIC
Congo, Rep.	LMIC
Côte d'Ivoire	LMIC
Equatorial Guinea	MHDC
Eritrea	LIC
Ethiopia	LIC
Gabon	HIHDC
Gambia, The	LIC
Ghana	LMIC
Guinea	LIC
Guinea-Bissau	LIC
Kenya	LMIC
Lesotho	LMIC
Liberia	LIC
Madagascar	LIC
Malawi	LIC
Mali	LIC
Mauritania	LMIC
Mozambique	LIC
Namibia	MHDC
Niger	LIC
Nigeria	LMIC
Rwanda	LIC
São Tomé and Príncipe	LMIC
Senegal	LIC
Sierra Leone	LIC
Somalia	LIC
South Africa	MHDC
South Sudan	LIC
Sudan	LMIC
Swaziland	LMIC
Tanzania	LIC
Togo	LIC
Uganda	LIC
Zambia	LMIC
Zimbabwe	LIC

Table legend

LIC	Low-income country, World Bank income classifications (June 2018)
LMIC	Lower middle-income country, World Bank income classifications (June 2018)
LDC	Least Developed Country, UN ECOSOC LDC list (March 2018)
LHDC	Low Human Development Country, UNDP Human Development Indices and Indicators (September 2018)
MHDC	Medium Human Development Country, UNDP Human Development Indices and Indicators (September 2018)
HIHDC	High Inequality in Human Development Country, UNDP Human Development Indices and Indicators (September 2018)
HIDBC	High Infectious Disease Burden Country, IHME Global Burden of Disease Study 2017 Results

APPENDIX VII

Appropriate Access: Product Scope and Definitions

PRODUCT SCOPE AND ELIGIBLE INDICATORS

- **On-patent antibacterial and antifungal medicines** – eligible indicators: C.1.1 - C.2.1.
- **Top 2 off -patent products by sales volume within each appropriate access category** – eligible indicators: C.1.2 – C.2.2.
  - Appropriate Access Categories: WHO AWaRe classification, tuberculosis medicines and antifungals.
  - [A]=Access group, [W]=Watch group, [R]=Reserve group, [T]=tuberculosis, [F]=antifungal.
- **On-patent antibacterial and antifungal vaccines – eligible indicators:** C.1.3 - C.2.3.
- All products were analysed by INN.

DEFINITIONS

Access strategy

[Working definition, used for analysis]

A strategy specifically intended to improve access to medicines or vaccines, that includes all the typical elements of a strategy (a clear rationale, targets, objectives and expected outcomes). In low- and middle-income countries where the company operates, the strategy may apply to a defined set of diseases, products, or therapeutic areas or to the whole portfolio.

Affordability

[Working definition, used for analysis]

The measure of a payer's ability to pay for a product (whether or not they are the end user). The Benchmark takes this into account when assessing pharmaceutical companies' pricing strategies.

Patient Reach

[Working definition, used for analysis]

The Benchmark evaluates the impact of companies' access strategies by looking for evidence of patient reach. Patient reach is defined by number of people benefitting from a specific access strategy or by the number of product units distributed.

Equitable Pricing Policy

[Working definition, used for analysis]

A targeted pricing strategy, which aims at improving access to medicines and vaccines for those in need by taking affordability for individuals and healthcare systems into account in a manner that is locally appropriate.

Donations

[Working definition, used for analysis]

A short- or long-term donation of products based on the expressed needs of a country. Donations may be made in emergency situations, such as conflict and natural disasters, or may be longer-term to control or eradicate a disease.

Patient Assistance Programme

[Working definition, used for analysis]

Patient assistance programmes are defined as programmes initiated by pharmaceutical companies which provide financial assistance or free-of charge medicines for a defined patient population with limited ability to pay.

Pooled-Procurement

[Working definition, used for analysis]

Pooled procurement is the formal arrangement where financial and nonfinancial resources are combined across different purchasing authorities to create a single entity for purchasing medicines or vaccines on behalf of individual purchasing authorities. Pooled procurement can be managed through a third-party such as the United Nations Children's Fund (UNICEF), Stop TB Partnership Global Drug Facility or the Pan American Health Organization (PAHO)[1].

Price Cap

[Working definition, used for analysis]

A price cap or price ceiling is a maximum price that can be charged for a product. A price cap is usually negotiated between a government and a pharmaceutical company to take affordability into account.

Public-Private Partnership

[Working definition, used for analysis]

A public-private partnership (PPP) is a partnership between one or more public organisations and the private sector for providing a public asset or service, in which the private party bears significant risk and management responsibility, and remuneration is linked to performance. The Benchmark also considers a partnership between a non-profit organisation and the private sector to be a PPP.

Tender

[Working definition, used for analysis]

A tender is a competitive procurement procedure to supply medicines or vaccines. The tendering process typically comprises price and volume requirements and is commonly used in many countries to encourage competition, particularly in lower-income countries or international agencies procuring on behalf of lower-income countries.1

Tiered Pricing Policy

[Working definition, used for analysis]

Tiered pricing, also known as differential pricing, refers to when differing classes of buyers are charged different prices for the same product. In the context of vaccines, low-and middle-income countries can be charged a reduced price compared to high-income countries[2].

Voluntary Licensing

[Working definition, used for analysis]

A voluntary license is an authorisation given by the patent holder to a generic company, allowing it to produce the patented medicine or vaccine, often at a lower cost. The license usually sets quality requirements and defines the countries in which the licensee can sell the product[3].

Direct Sales Contract

[Working definition, used for analysis]

A direct sales contract is an agreement between a pharmaceutical company and a buyer. The pharmaceutical company agrees to supply its medicines or vaccines to the buyer at a specified price. The contract may be for a specific volume or for a specific contract period. Direct sales are often used by generic manufacturers to expand access to their generic medicines, and the buyers may be, but are not limited to, distributors or hospitals in the public or private sector.

REFERENCES

1 WHO. WHO Guideline on Country Pharmaceutical Policies.; 2020. Accessed October 14, 2021. file:///C:/Users/Diane/Downloads/9789240011878-eng.pdf

2 The World Bank and GAVI Alliance. Immunization Financing Toolkit.; 2010. Accessed October 14, 2021. https://www.who.int/immunization/programmes_systems/financing/analyses/Brief_14_Tiered_Pricing.pdf

3 IFPMA. Voluntary licenses and non-assert declarations. Published online 2010. Accessed October 14, 2021. https://www.ifpma.org/resource-centre/voluntary-licenses-and-non-assert-declarations/

APPENDIX VIII

Guide to Report Cards

The Guide to Report Cards provides a description of each section of the Report Cards for the 2021 Antimicrobial Resistance Benchmark.

Section	Description	Source
General company information (header)	Company name, Stock exchange(s), Ticker(s), Location of headquarters, Number of employees (as a total)	• Annual report for the fiscal year ending 31 December 2020 or later (or, equivalently, forms 10-K or 20-F) • Company website
Performance in the Benchmark (figure)	This figure shows the company's overall score.	• Benchmark analysis
Performance by Research Area	This figure shows the company's score for each of the Research Areas in which it was scored.	• Benchmark analysis
Performance (text)	This section summarises the company's overall performance in the Benchmark. It covers: • Drivers behind its scores • Main areas where the company scores well or below average compared to peers	• Benchmark analysis
How company was evaluated: (by indicator)	This figure shows the indicators that were applicable to the company.	• Benchmark Methodology Report 2020 • Benchmark analysis
Opportunities (text)	This section outlines opportunities for the company to do more to address AMR. The opportunities listed take into account company-specific characteristics.	• Benchmark analysis
Changes since 2020	This section provides an update on the most notable changes on the company's actions to curb AMR since the 2020 Benchmark. It includes a selection of new or expanded commitments, strategies, activities, and programmes. These updates may have taken place after the period of analysis and are not necessarily scored by the Benchmark.	• Benchmark analysis • Public sources, such as company website or press releases
Sales and Operations (text)	**Therapeutic areas**: Therapeutic areas the company focuses on, as available in public sources. **Business segments**: How the company is operationally organised, as presented in official company sources. **Product categories**: Types of products the company markets, as available in public sources, and standardised by the Benchmark across companies. **M&A since 2018**: Merger & acquisition activity since 2020 specifically relevant for antibacterial or antifungal products.	• Annual report for the fiscal year ending 31 December 2020 or later (or, equivalently, forms 10-K or 20-F) • Company website • Press releases by company or news websites • Stock exchange communications
Revenues by product (figure)	This figure shows, where possible, a breakdown of the company's revenues in fiscal year 2020 into: antibacterial and antifungal medicines; antibacterial vaccines; other pharmaceuticals; other (non-pharmaceuticals). If such breakdown is not possible, categories are based on companies' business segments or may show only the total revenue.	• Annual reports for the fiscal years 2019 and 2020 (or, equivalently, forms 10-K or 20-F)
Revenues by region (figure)	This figure shows a breakdown of the company's revenues by geographic region in fiscal year 2020. The categories are based on official company reports but may be aggregated. If no breakdown by region is possible, the figure shows only the total revenue. If this is the case for both the regional and product breakdowns, there is a single figure showing the total revenue.	• Annual reports for the fiscal years 2019 and 2020 (or, equivalently, forms 10-K or 20-F)

Pipeline (text)	This section describes the R&D pipelines of the Large Research Based Pharmaceutical companies for pathogens in scope with respect to the following points:
	
	Pipeline size: Provides the total number of projects in scope, including a breakdown by type.
	
	Development stages: Provides a count of the company's projects in clinical stage (listing examples), followed by a count of projects in discovery or pre-clinical stage.
	
	Novelty: Lists projects that are considered novel by the Benchmark, as per the WHO innovativeness criteria and PEW charitable trusts (see Sources column).
	
	'Critical' and/or 'urgent' pathogens: Lists projects that target pathogens defined as 'critical' by WHO's list of priority pathogens and/or characterised as 'urgent' threats by the US Centers for Disease Control and Prevention (CDC).
	
	Regulatory approvals: Lists regulatory approvals for projects targeting priority pathogens between 22 June 2019 and 15 October 2021.
		• Benchmark pipeline analysis
		• The WHO innovativeness criteria are listed in:
		  • 2020 Antibacterial agents in clinical and preclinical development: an overview and analysis. Geneva: World Health Organization; 2021.
		  • 2019 Antibacterial agents in clinical development: an analysis of the antibacterial clinical development pipeline. Geneva: World Health Organization; 2019.
		  • Antibacterial agents in preclinical development: an open access database. Geneva: World Health Organization; 2019.
		• The Pew Charitable Trusts: Antibiotics currently in global clinical development – Mar 2021 update
		• The Pew Charitable Trusts: Nontraditional Products for Bacterial Infections in Clinical Development – Apr 2021 update.

Pipeline for priority pathogens (figure)	This figure shows, where possible, a breakdown of the company's pipeline for pathogens in scope, including projects in antibacterial vaccines; antibacterial medicines; antifungal vaccines; and antifungal medicines.	• Benchmark pipeline analysis. • Company website and clinical trials registries.
Portfolio (text)	This section describes a company's antibacterial and antifungal product portfolio, starting with a comparative statement on the number of products (INN-level) in scope, including a breakdown by type. The total number of products reflects the INN only and not the different formulations. The following information is also listed, as applicable: • **On-patent medicines** • **On-patent vaccines** • **Off-patent/generic medicines** • **AWaRe medicines:** Number of medicines in each WHO AWaRe group for antibacterials (Access, Watch, Reserve) • **Anti-TB medicines:** Number of anti-tuberculosis medicines The classification of products as "Anti-TB medicines" follows the 2019 WHO EML. For products with a square box, alternative products listed on ATC/DDD Index 2021 are also treated as on EML.	• Benchmark Portfolio Analysis • Registered products identified from the EMA, FDA, and the company's website. • IQVIA MIDAS® 2017 anti-infectives data • WHO EML, 21st List, 2019 • WHO and the Norwegian Institute of Public Health, ATC/DDD Index 2021; https://www.whocc.no/atc_ddd_index/ • Appendix II of the Benchmark Methodology Report 2019 (Products in Scope for Access Indicators)
Products on the market (figure)	This figure shows, where possible, a breakdown of the company's marketed products in scope by antibacterial vaccines; antibacterial medicines; and antifungal medicines. The number of products is based on data from public sources, IQVIA MIDAS®, and data verified by the company. It may not account for the company's entire product portfolio.	• Company verification • Registered products identified from the EMA, FDA, and the company's website • IQVIA MIDAS® 2017 anti-infectives data

Performance by Research Area: **A. Research & Development (text)**	This section summarises company performance for the Research Area of Research & Development, by indicator. The paragraphs describe the company's performance and highlight (where available) relevant examples of its activities. In indicator A.2.2, novelty is analysed for clinical-stage medicine projects only and based on criteria defined by the WHO and PEW charitable trusts (see Sources column). In indicator A.2.4, the assessment is based on the number of unique candidates (i.e., unique INNs) within the projects that target critical or urgent priorities. In indicator A.3, detailed portfolio-wide or project-specific access and stewardship plans are analysed for late-stage projects only. This includes projects in clinical Phase II or III, as well as projects awaiting approval or approved during the period of analysis (2019/06/22 to 2021/04/30) but not Phase IV or technical lifecycle projects. For medicine projects, the Benchmark looks at both access and stewardship plans, whereas for vaccine projects, where overuse or inappropriate use is not a concern with respect to AMR, only access plans are considered.	• Benchmark pipeline analysis • 2020 Antibacterial agents in clinical and preclinical development: an overview and analysis. Geneva: World Health Organization; 2021. • 2019 Antibacterial agents in clinical development: an analysis of the antibacterial clinical development pipeline. Geneva: World Health Organization; 2019. • Antibacterial agents in preclinical development: an open access database. Geneva: World Health Organization; 2019. • The Pew Charitable Trusts: Antibiotics currently in global clinical development – Mar 2021 update. • The Pew Charitable Trusts: Nontraditional Products for Bacterial Infections in Clinical Development – Apr 2021 update.
Pipeline targeting pathogens in scope (figure)	This figure shows the company's pipeline of antibacterial and antifungal medicines and vaccines targeting priority pathogens. Phase IV projects, technical lifecycle projects are not shown. Where applicable, regulatory approvals (including label extensions) are noted, including the regulatory body/location and date of approval. Data omissions due to confidentiality agreements are noted. Although the figure shows the pipeline as of September 2021, the analysis in the R&D Performance by RA text considers the status of projects at the end of the period of analysis, on 30 April 2021.	• Projects submitted by the company for scoring and analysis in the Benchmark, including verification/cross- reference with publicly available pipeline information. Approval data is verified using public sources, e.g., clinical trial registries or press releases by companies.
Performance by Research Area: **B. Responsible Manufacturing (text)**	This section summarises company performance for the Research Area of Responsible Manufacturing, by indicator. The paragraphs describe the company's performance and highlight (where available) relevant examples of its activities. In indicator B.2, discharge limits published in the AMR Industry Alliance website were also considered in the assessment, despite not qualifying as disclosure via an official individual company source. In indicator B.3, three public databases were searched: the FDA inspection classification database, EMA EudraGMP database and WHO notice of concern database (see Sources column).	• Benchmark analysis • Official public company sources such as annual or CSR reports, CDP Water Security reports, policy documents or company websites • FDA inspection classification database (https://www.fda.gov/inspection-classification-database) • EMA EudraGMP database (http://eudragmdp.ema.europa.eu/inspections/displayWelcome.do) • WHO notice of concern database https://extranet.who.int/pqweb/inspection-services/notice-concern
Performance by Research Area: **C. Appropriate Access (text)**	This section summarises company performance for each Access indicator in the Research Area of Appropriate Access and Stewardship. The paragraphs describe the company's performance and highlight (where available) relevant examples of its activities. In indicators C.1.1 and C.2.1, "on-patent products" refers to all on-patent antibacterial and antifungal medicines and vaccines that the company markets. In indicators C.1.2 and C.2.2, "off-patent products" refers to a company-specific set of off-patent antibacterial and antifungal medicines based on each company's highest volume sales data globally and in 21 low-income markets, as provided by IQVIA Midas® 2017 database. Products were first derived from the 2017 WHO EML and divided into six categories: four based on the 2017 WHO AWaRe classification of Access, Watch, Access/Watch and Reserve and two for antifungals and anti-tuberculosis medicines. Indicator C.3 considers all antibacterial and antifungal medicines and vaccines in scope for this Benchmark.	• Benchmark analysis • IQVIA MIDAS® 2017 anti-infectives data • Company websites • WHO EML, 20th List, 2017 • WHO EML, 21st List, 2019 • Appendix II of the Benchmark Methodology Report 2019 (Products in Scope for Access Indicators)

Performance by Research Area: **C. Stewardship (text)**	This section summarises company performance for each Stewardship indicator in the Research Area of Appropriate Access and Stewardship. The paragraphs describe the company's performance and highlight (where available) relevant examples of its activities. Only antibacterial and antifungal medicines are in scope for this Research Area. The geographic scope is global.	• Benchmark analysis • Public sources such as company websites or independent 3rd party websites • Public sources such as the AMR Register (https://amr.theodi.org/) which is sharing surveillance data. • AMR Industry Alliance website (https://www.amrindustryalliance.org/)

APPENDIX IX

Figures

APPENDIX X

Definitions

Access plan
[Working definition, used for analysis]
An access plan is a plan set up to ensure that public health needs are taken into consideration during R&D. These plans may be developed in-house or through collaborations and include commitments, strategies, concrete provisions and other agreed-upon measures (typically developed in partnership) to enforce accountability. Access plans facilitate availability, accessibility and affordability for patients in countries within the scope of the Benchmark (e.g., registration commitments, equitable pricing strategies, sufficient supply commitments, non-exclusivity in specified territories, waiving of patent rights, royalty-free provisions and applying for WHO prequalification).

Active pharmaceutical ingredient (API)
The active pharmaceutical ingredient (API) is the active pharmaceutical component of a medicine that carries out its intended effects. Some medicines, such as combination therapies, have multiple active ingredients that target multiple disease pathways and/or symptoms. The inactive ingredients of a medicine are referred to as excipients.

Adaptive R&D
[Working definition, used for analysis]
R&D adaptations to existing medicines and/or vaccines. This includes new formulations, new fixed-dose combinations of existing chemical or biological entities, a new target demographic, or the repurposing of an existing product for additional indications.

AMR surveillance
[Working definition, used for analysis]
The continuous and systematic collection, analysis and interpretation of antimicrobial infection and resistance-trend data needed for the planning, implementation, and evaluation of antimicrobial stewardship activities.

Antibacterial medicine
[Working definition, used for analysis]
Antimicrobial medicine used to treat bacterial infections by directly targeting the bacteria that causes the infection or the disease process (as opposed to targeting the symptoms of the infection). Biocides are not considered antibacterial medicines See also Antibiotic medicine.

Antibacterial resistance
Antimicrobial resistance occurring specifically in bacteria. This resistance renders the medicines normally used to treat bacterial infections (e.g., urinary tract infections, pneumonia, bloodstream infections) ineffective. Sometimes also referred to as antibiotic resistance. See also antimicrobial resistance.

Antibiotic medicine
[Working definition, used for analysis]
Equivalent to Antibacterial medicine. The term "antibiotic" is used inconsistently in the literature to denote either a drug that targets any type of microorganism in the body or, alternatively, a drug that targets bacteria specifically. Given the ambiguity, the Benchmark preferably avoids use of this term, referring to the more general category as "antimicrobial" and to the more specific one as "antibacterial".

Antifungal medicine
[Working definition, used for analysis]
Antimicrobial medicine used to treat fungal infections by directly targeting the fungi that causes the infection (as opposed to targeting the symptoms of the infection or toxins produced by the pathogen).

Antimicrobial medicine
[Working definition, used for analysis]
A medicine used to treat an infectious disease by directly targeting the bacteria, fungi, helminths, protozoa, or viruses that cause the infection (as opposed to targeting the symptoms of the infection or toxins produced by the pathogen).

Antimicrobial resistance (AMR)
Antimicrobial resistance is the ability of microbes such as bacteria, viruses, fungi and parasites (protozoa or helminths) to grow in the presence of an antimicrobial substance (e.g., a medicine) that would normally kill them or limit their growth. Resistance is a consequence of evolution via natural or artificial selection.

Antimicrobial stewardship
A systematic and comprehensive process that aims to ensure that all aspects of prescribing, (e.g., drug, dose, duration), dispensing, and the use of antimicrobial medicines are consistent with the available evidence on how to minimise the emergence of antimicrobial resistance.

Appropriate use of antimicrobials
The cost-effective use of antimicrobials, which maximises clinical therapeutic effect while minimising both drug-related toxicity and the development of antimicrobial resistance [WHO Global Strategy for Containment of Antimicrobial Resistance, 2001].

Broad-spectrum antibacterial
Broad-spectrum antibacterial medicines are active against a wide range of bacterial types and may be used to treat a wide range of bacterial infections.

Capacity building
The company forms partnerships with local stakeholders to increase capacity (e.g. by training of staff or obtaining equipment and other necessary resources) in order to strengthen the supply chain.

Clinical-stage drug development
[Working definition, used for analysis]
Clinical-stage drug development comprises phases I through III of clinical development. Products approved (or awaiting approval) between 22 June 2020 (end of the period of analysis for the previous edition of the Benchmark) and 30 April 2021 are also categorised as late-stage.

Conflict of interest (COI)
[Working definition, used for analysis]
Within the context of pharmaceutical companies' engagement in public health-oriented initiatives, a conflict of interest potentially arises when the commercial interests of the company conflict with the primary interest of protecting and promoting public health.

Cross-resistance
Cross-resistance refers to the resistance developed to a usually effective antimicrobial medicine through exposure to a similarly acting substance. Cross-resistance can occur among human antimicrobials and is also observed between human antimicrobials and products used in animal health or agriculture (e.g., pesticides, herbicides or fungicides).

Disability-Adjusted Life Year (DALY)
The disability-adjusted life year (DALY) is a measure of disease burden that combines disease-associated mortality and morbidity. It is the sum of the number of years of life lost (YLLs) and years lived with disability (YLDs). DALYs allow comparison of disease burden across different populations and health conditions across time. One DALY equals one lost year of healthy life.

Drug product
The finished dosage form of a medicine obtained at the end of the manufacturing process, (e.g., the tablet, capsule, or solution containing the active pharmaceutical ingredient(s), generally, but not necessarily, in association with one or more other ingredients). Also referred to as a finished drug product, finished product or formulation.

Environmental risk management (ERM)
[Working definition, used for analysis]
In the context of antibacterial product manufac-

turing, environmental risk management (ERM) seeks to determine and manage environmental risks resulting from the production of antibacterials, such as the emergence of antibacterial resistance, to protect human health and the environment.

Falsified medicine
A medicine which is deliberately and fraudulently mislabelled with respect to identity and/or source. Falsified medicines may contain no active ingredient, the wrong active ingredient or the wrong amount of the correct active ingredient.

Generic medicine
A medicine that is created to be the same as a known marketed brand-name drug (the originator medicine) in dosage form, strength, route of administration, quality and performance characteristics, and intended use. See also Originator medicine.

Good Manufacturing Practices (GMP)
Good manufacturing practice (GMP) is a system employed to ensure that products are consistently produced and controlled according to appropriate quality standards. Within pharmaceutical production this serves to minimise risks such as unexpected contamination, incorrect labelling or incorrect dose of the active ingredient. GMP covers all aspects of pharmaceutical production (e.g., starting materials, premises, equipment, training and personal hygiene of staff) and includes processes that provide documented proof that correct procedures are consistently followed at each step of the manufacturing process. GMP guidelines are established and overseen by regulatory agencies in individual countries or regions, as well as the WHO.

Healthcare Professional (HCP)
Any specialised worker in any branch of healthcare that provides preventive, curative or rehabilitative services to the community.

Intellectual capital
[Working definition, used for analysis]
Intellectual capital is the intangible value of a company, covering its employees (human capital), its relationships (relational capital) and the infrastructure (e.g. hardware, software, databases, processes, patents) that supports the work of its employees (structural capital). A company's intellectual capital gives it a competitive advantage. In the context of the Benchmark, the intellectual capital of a pharmaceutical company may comprise of, for example, molecule libraries, patented compounds, processes and technologies or unpublished data on pharmacological characteristics of compounds.

International non-proprietary name (INN)
The International non-proprietary name (INN) is a common, generic name selected by designated experts for the unambiguous identification of a pharmaceutical substance or active pharmaceutical ingredient. The selection process is coordinated by World Health Organization (WHO) via its INN Programme. Each INN is a unique name that is globally recognised and is public property.

Late-stage drug development
[Working definition, used for analysis]
In the context of the pharmaceutical R&D pipeline, medicine and vaccine candidates in Clinical phase II or Clinical phase III are considered to be in late-stage clinical development. Products approved (or awaiting approval) between 22 June 2020 (end of the period of analysis for the previous edition of the Benchmark) and 30 April 2021 are also categorised as late-stage by the Benchmark.

Narrow-spectrum antibacterial
Narrow-spectrum antibacterials are antibacterial medicines that are active against a selected group of bacterial types. Examples include colistin, an antibacterial that selectively targets gram-negative bacteria, and vancomycin, an antibacterial that selectively targets gram-positive bacteria.

Novel drug candidate
[Working definition, used for analysis]
A novel candidate meets at least one of the four criteria defined in WHO's report "2020 Antibacterial agents in clinical and preclinical development" (2021): (1) new chemical class; (2) new target; (3) new mode of action; (4) absence of cross-resistance. This assessment is applied only to candidates in clinical stage and validated by WHO and/or external experts.

Off-patent medicine
[Working definition, used for analysis]
A medicine whose granted patent protection has expired. Patent protection typically lasts for 20 years and is specific to each country.

On-patent/patented medicine
[Working definition, used for analysis]
A patented or on-patent medicine is one which has received exclusivity rights, allowing the patent holder to prevent or stop others from making, using, selling or importing the medicine within the country that granted the patent. The Benchmark determines patent status for its products in scope through a process that combines data from selected regulatory authority websites (e.g. FDA) and participating companies.

One Health
An approach used to design and implement public health programmes, policies, legislation and research in which multiple sectors communicate and work together to achieve better outcomes. The areas for which a One Health approach is particularly relevant include food safety, the control of zoonosis, and combating antimicrobial resistance. [WHO, 2017]

Originator medicine
The medicine that was first authorised worldwide for marketing, normally as a patented product, on the basis of its documented efficacy, safety and quality, according to requirements at the time of authorisation. The originator medicine always has a brand name; this name may, however, vary among countries.

Over-the-counter medicine
A medicine that can be purchased without prescription from a healthcare professional.

Period of analysis
[Working definition, used for analysis]
The 2021 AMR Benchmark report will assess company activities taking place during a period of analysis going from 22 June 2020 to 30 April 2021. For the R&D research area, projects need to be ongoing, approved or awaiting approval by the end of the period of analysis.

Preclinical-stage drug development
[Working definition, used for analysis]
Preclinical-stage drug development comprises the discovery and preclinical phases of drug development.

Predicted no-effect concentration (PNEC)
In the context of environmental risk assessment, the predicted no-effect concentration (PNEC) is the concentration of a substance in any environment below which adverse effects will most likely not occur. The PNEC can be based on acute (short-term) or chronic (long-term) toxicity data and usually takes account of the uncertainty in extrapolating from collected/available data to the entire ecosystem.

Priority pathogen
[Working definition, used for analysis]
Priority pathogens are pathogens for which new medicines and vaccines are highly needed. The Benchmark identified this set of priority pathogens based on the WHO priority pathogens list as of 15 January 2020 and the CDC's US Biggest Threats list as of December 2019.

Product Development Partnership (PDP)
[Working definition, used for analysis]
Product Development Partnerships (PDPs) take the form of centralised non-profit organisations that facilitate financial risk-sharing across the public and private sectors by pooling and sharing resources, both tangible and intangible, for the development of medicines, vaccines, and other health tools.

Public-private partnership
[Working definition, used for analysis]
A public-private partnership (PPP) is a partnership between one or more public organisations and the private sector for providing a public asset or service, in which the private party bears significant risk and management responsibility, and remuneration is linked to performance. The Benchmark also considers a partnership between a non-profit organisation and the private sector to be a PPP.

Pull incentive
Pull incentives, in the form of extended exclusivity periods, higher reimbursement or market entry rewards, reward companies for bringing new drugs to the market through lowering the uncertainty for return on investment.

Push incentive
Push incentives, in the form of grants, partnerships or tax credits, are employed to lower the cost of and de-risk research and development of a new medicine.

Responsible promotional practices
[Working definition, used for analysis]
Promotional activities targeting the general public, patients, and healthcare professionals in such a way that transparency, integrity, accuracy, clarity and completeness of information can be ensured.

Stewardship plan
[Working definition, used for analysis]
A stewardship plan is a plan set up to ensure that AMR-relevant public health needs are taken into consideration during R&D. These plans may be developed in-house or through collaborations and include commitments, strategies, concrete provisions, and other agreed-upon measures (typically developed in partnership) to enforce accountability. Stewardship plans facilitate the appropriate use of antimicrobial medicines and reduce the emergence of resistance. Examples include (but are not limited to) appropriate promotional practices and conducting surveillance studies.

Substandard medicine
Also referred to as "out of specification", these are market-authorised medicines that fail to meet either quality standards or specifications, or both. [based on WHO, 2017]

Zero-liquid discharge (ZLD)
ZLD is a waste-treatment process in which a manufacturing site does not discharge any water into the environment as this will be reused and recycled while solid residue is incinerated or sent to landfill. [Ranade & Bhandari, 2014].

Report Design
Explanation Design (Klaas van der Veen)
Production i.c.w. Marloes van Dijken, Mark Bakker

Photo Disclaimer
The Access to Medicine Foundation gratefully respects the permission granted to reproduce the copyright material in this report. Every reasonable effort has been made to trace copyright holders and to obtain their permission for the use of copyright material. Should you believe that any content in this report does infringe any rights you may possess, please contact us at info@accesstomedicinefoundation.org or + 31 (0) 20 21 53 535.

Disclaimer
As a multi-stakeholder and collaborative project, the findings, interpretations and conclusions expressed herein may not necessarily reflect the views of all members of the stakeholder groups or the organisations they represent. The report is intended to be for information purposes only and is not intended as promotional material in any respect. The material is not intended as an offer or solicitation for the purchase or sale of any financial instrument. The report is not intended to provide accounting, legal or tax advice or investment recommendations. Whilst based on information believed to be reliable, no guarantee can be given that it is accurate or complete.