ANTIMICROBIAL RESISTANCE (AMR) PROGRAMME

Methods matter: What steps are companies taking to help curb AMR by manufacturing responsibly?

AUGUST 2023

The discharge of antibiotic waste that contains active pharmaceutical ingredients into the environment is one of the drivers of antimicrobial resistance (AMR), which is a hugely significant threat to global public health. By responsibly managing and disposing of their antibiotic manufacturing waste, pharmaceutical companies can help curb the development and spread of AMR. Some companies are already taking steps to employ responsible manufacturing practices, however, more needs to be done to make a greater impact in the fight against AMR. This report highlights three areas companies can focus on to boost their efforts.

access to medicine FOUNDATION

ACKNOWLEDGEMENTS

The Access to Medicine Foundation would like to thank the following people and organisations for their support.

FUNDERS

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

Ministry of Health, Welfare and Sport

AUTHORS

Martijn van Gerven
Fatema Rafiqi

EDITORIAL TEAM

Jana Jacobs

EXPERT REVIEWERS

Joakim Larsson, University of Gothenburg;
Mark Montforts, RIVM, the Dutch National Institute for Public Health and the Environment

ACCESS TO MEDICINE FOUNDATION

The Access to Medicine Foundation is an independent non-profit organisation that seeks to transform the healthcare ecosystem by motivating and mobilising companies to expand access to their essential healthcare products in low- and middle-income countries.

Naritaweg 227-A
1043 CB, Amsterdam
The Netherlands

For more information about this publication, please contact
Marijn Verhoef, Director of Operations and Research
mverhoef@accesstomedicinefoundation.org
+31 (0) 20 215 35 35
www.accesstomedicinefoundation.org

Table of contents

About this report

This report is part of the Access to Medicine Foundation's Antimicrobial Resistance (AMR) Programme, which works to move pharmaceutical companies in responding to the growing challenge of drug-resistant infections. The AMR Programme's publications – including both the AMR Benchmark (published in 2018, 2020 and 2021) and targeted thematic reports such as this – focus on how pharmaceutical companies perform in terms of taking action on identified priorities to address AMR.

HOW THIS REPORT WAS DEVELOPED

The case studies, discussion and recommendations in this report have been drawn from research published in the 2021 AMR Benchmark, as well as from recent interviews with selected companies. Consultations were also held with relevant expert stakeholders, including procurement organisations, investors, academia and policymakers. The report was further informed by sources available in the public domain, including peer-reviewed literature, company and global health reports, policy literature and government documents. The information collected from the sources was cross-checked to ensure accuracy, including directly with companies and other stakeholders, as appropriate and relevant.

SCOPE OF THE RESEARCH

COMPANIES

This report includes case studies on pharmaceutical companies – including large research-based companies, generic medicine manufacturers and business-to-business suppliers – that manufacture antibiotics and antifungal medicines. It considers both a) companies' directly operated manufacturing sites, and b) companies' third-party supplier sites. The following companies are specifically mentioned in the report: Abbott; Aurobindo; Centrient; Fresenius Kabi; GSK; Pfizer; Novartis and its generics unit, Sandoz*; Shionogi; Teva, and Viatris. Data was also analysed from the following companies' previous submissions to the 2021 AMR Benchmark: Alkem, Cipla, Hainan Hailing, Johnson & Johnson, MSD, Otsuka, Sanofi and Sun Pharma.

PRODUCTS

This report looks at marketed antibiotic and antifungal medicines.

*Novartis has announced that it will separate its generics division, Sandoz, into a standalone company by way of a 100% spin-off, planned for Q4 2023.[1]

Executive summary

Antimicrobial resistance (AMR) is a serious global health threat that already kills millions of people worldwide each year. And the threat is growing.

Tackling this urgent issue requires comprehensive approaches that target the various drivers of drug resistance. While the overuse and misuse, as well as lack of access to appropriate antibiotics, are among the well-known drivers of AMR, it is becoming increasingly clear that releasing antibiotic waste into the environment can also fuel rising drug resistance.

When antibiotics are manufactured, waste that is generated is discharged into the environment – particularly into rivers that are used for drinking water and agriculture. If this waste contains high levels of active pharmaceutical ingredients (APIs), it poses a serious risk to the emergence and spread of AMR while also causing environmental harm.

It is therefore vital that pharmaceutical companies engage in responsible manufacturing practices that ensure their lifesaving medicines are produced in a way that does not – as an unintended consequence – have a detrimental impact on human health and the environment.

Pharmaceutical companies play a critical role in reducing the impact of antibiotic waste in the environment

Globally, antibiotic manufacturing supply chains are complex, involving multiple producers that supply partners with APIs and drug products. At the same time, the supply chains for antibiotics are also highly fragmented. There are several important upstream supply stages, with many suppliers available at some of these points, and very few at other vital stages – with the consequence that there is often a heavy reliance on a limited number of producers of a certain API, for example.

Among the various players across antibiotic manufacturing supply chains, pharmaceutical companies with marketing authorisations are among the largest, and can have the biggest impact on transforming the industry. Not only do they frequently operate their own manufacturing sites, but they also contract a wide range of third-party suppliers, manufacturers, wholesalers, and retailers. Pharmaceutical companies are therefore uniquely positioned to influence and shape responsible manufacturing practices across the supply chain – starting at their own manufacturing sites.

However, previous research by the Access to Medicine Foundation – as part of the 2021 Antimicrobial Resistance (AMR) Benchmark – has found that many pharmaceutical companies have not yet taken effective action to address AMR risks in their manufacturing processes and supply chains.

To support and enable progress, the Foundation has developed this report. By zeroing in on responsible manufacturing practices, it identifies specific areas that companies need to focus on, and the steps they can take, to develop and maintain solutions that will help them limit their antibiotic waste more effectively.

INSIGHTS

The company examples assessed in this report clearly illustrate that it is possible for companies – regardless of size – to take progressive steps in implementing responsible manufacturing practices at their own manufacturing sites and those of their suppliers.

Companies with ≥ 10 directly operated manufacturing sites:

- GSK reports that 100% of supplier sites are compliant with discharge limits, while Pfizer reports this for over 86% of its supplier sites.
- Abbott offers support for its contracted manufacturing suppliers in conducting wastewater analysis more efficiently, free of charge.
- GSK, Teva and Viatris publicly report specific details of their waste management practices.

Companies with < 10 directly operated manufacturing sites:

- Centrient reports that 100% of its supplier sites are compliant with discharge limits, while Shionogi reports this for 71% of its supplier sites.
- In consultations for this report, Shionogi stated achieving compliance directly in its wastewater for all five antibiotics it manufactures: cefiderocol, flomoxef, latamoxef, doripenem and cefcapene pivoxil.
- Centrient implements a comprehensive waste-treatment process to achieve end-of-pipe compliance at its site in Toansa, India.
- Centrient and Shionogi publicly report specific details of their waste management practices, with Shionogi disclosing the status of compliance with discharge limits and location of its suppliers.

Steps companies can take to ensure they manufacture responsibly

The company examples analysed in this report demonstrate the feasibility of progressing in these areas – with recommendations aimed at guiding leaders on how to boost their efforts, and showing others what they need to do to step up.

Firstly, companies need to prioritise effective wastewater management methods to establish, quantify and monitor discharge limits for ensuring their wastewater safety.

A discharge limit indicates the highest concentration of APIs that can be present in wastewater at which no resistance is expected to occur. Among the companies evaluated in the 2021 AMR Benchmark, those that quantify APIs all carry out such estimations after their wastewater has been released into a river or waterway. However, this means that the estimated concentrations will be diluted. It is, rather, in undiluted wastewater where bacteria are first exposed to antibiotic waste, with the risk of resistance already occurring here. If companies were to comply with limits before releasing their wastewater (i.e., assessing concentrations before they are diluted in a river, for example), this could significantly reduce the risk of exposing bacteria to APIs.

To date, no company reports actively applying discharge limits in their wastewater before releasing it. In fact, many companies are still struggling to achieve compliance with limits in rivers, let alone before releasing wastewater. However, two companies in scope of this report demonstrate clear, effective approaches to mitigating AMR risk in wastewater before releasing it into the environment. Both Centrient and Shionogi utilise extensive and comprehensive waste treatment processes to ensure wastewater safety, with Centrient also conducting regular monitoring of its wastewater by taking monthly wastewater samples and testing antibiotic concentrations each quarter.

These examples demonstrate that even though reaching full compliance of wastewater before it is released into the environment may be a longer-term endeavour, it is possible for companies to try and maximise their efforts to ensure the safety of their wastewater before discharging it.

Secondly, companies can utilise their unique positions in the antibiotic supply chain to transform the industry.

Over and above employing effective waste management practices at their own manufacturing sites, companies can also ensure that their suppliers comply with discharge limits, as demonstrated by four companies in scope of this report. Centrient, GSK, Shionogi and Pfizer report that either the majority of their suppliers, or all of them, comply with discharge limits set for the receiving environment.

To hold suppliers accountable, companies can, for example, include contractual clauses and provisions to comply with discharge limits to reduce AMR risk. Where possible, companies can enforce such contracts with non-compliant suppliers and seek an alternative supplier, as available.

However, given that there are often limited suppliers for certain APIs and drug products, companies consulted for this report stated that they prefer to build long-term relationships with suppliers. Notably, Abbott demonstrates this by offering support for its contracted manufacturing suppliers in conducting wastewater analysis more efficiently, free of charge.

If more companies take proactive steps to support their suppliers in such practical ways, we will see responsible manufacturing progress without jeopardising sustainable and secure supply of antibiotics to patients.

Finally, it is crucial for companies to ensure transparency and accountability along the supply chain.

When companies take action to mitigate AMR risks through responsible manufacturing, it is critical that they provide clear information about the initiatives and processes that are being implemented at their own manufacturing sites, and how they are monitoring supplier compliance. Not only will this allow for accountability across the supply chain, but it can offer much-needed insights into the relationship between wastewater management and AMR.

However, overall transparency along the supply chain is currently lacking. While some companies assessed by the AMR Benchmark and this report do disclose whether they meet discharge limits, for example, they do not provide clarification on how they achieve this, such as details on how concentrations are quantified. This information can, for example, be valuable in helping experts and other stakeholders gain a better understanding of the link between AMR and manufacturing.

Centrient, GSK, Shionogi, Teva and Viatris are the only companies to publicly report specific details on their waste management practices. However, none of these companies, or any others, report actual antibiotic discharge levels (at their own or suppliers' sites).

What's next?

At present, the regulatory landscape is underdeveloped and – across the world – there is no regulation specifically targeting antibiotic discharge from manufacturing sites to help limit AMR. In the absence of regulation, the onus is largely on pharmaceutical companies to take voluntary action and seize opportunities to reduce their impact on the environment and AMR. As this report identifies, there are a handful of leading companies that demonstrate that this is entirely possible. However, overall industry efforts are still not going far enough, and more companies will have to step up.

Moreover, with AMR gaining prominence on multilateral and national agendas, stakeholders – including governments, regulators, procurers, and investors – are focusing more keenly on the risks of AMR from manufacturing and are increasingly expecting companies to demonstrate responsible manufacturing practices.

Beyond taking responsibility for curbing AMR, the final section of this report explains why companies need to proactively adopt and scale responsible manufacturing practices from a business and operational perspective.

Procurers, for example, who can consider criteria related to the environment and sustainability when making purchasing decisions, are increasingly expecting companies to demonstrate comprehensive and effective practices to limit antibiotic waste. More investors also now view AMR as a systemic risk that needs to be considered within environmental, social and governance (ESG) standard-setting and reporting frameworks. There are also signs that regulation aimed at reducing AMR risk from manufacturing may be introduced, or strengthened, in several countries.

For companies that prioritise their environmental impact, and recognise their role in tackling global health issues, responsible manufacturing can further ensure their sustainability within a global health landscape that is increasingly focusing on AMR and the factors that fuel it.

By acting now and investing in responsible manufacturing, companies will not only help curb this global health threat, but can set themselves apart in the market.

Current state of play

Antimicrobial resistance (AMR) is rising fast and, as of 2019, the World Health Organization (WHO) has declared it to be one of the top ten global public health threats facing humanity.[2] In 2019 alone, the deaths of 1.27 million people were directly attributed to antimicrobial-resistant infections, and it is the people living in the world's poorest countries that experience severe levels of AMR and the highest rates of infectious disease.[3]

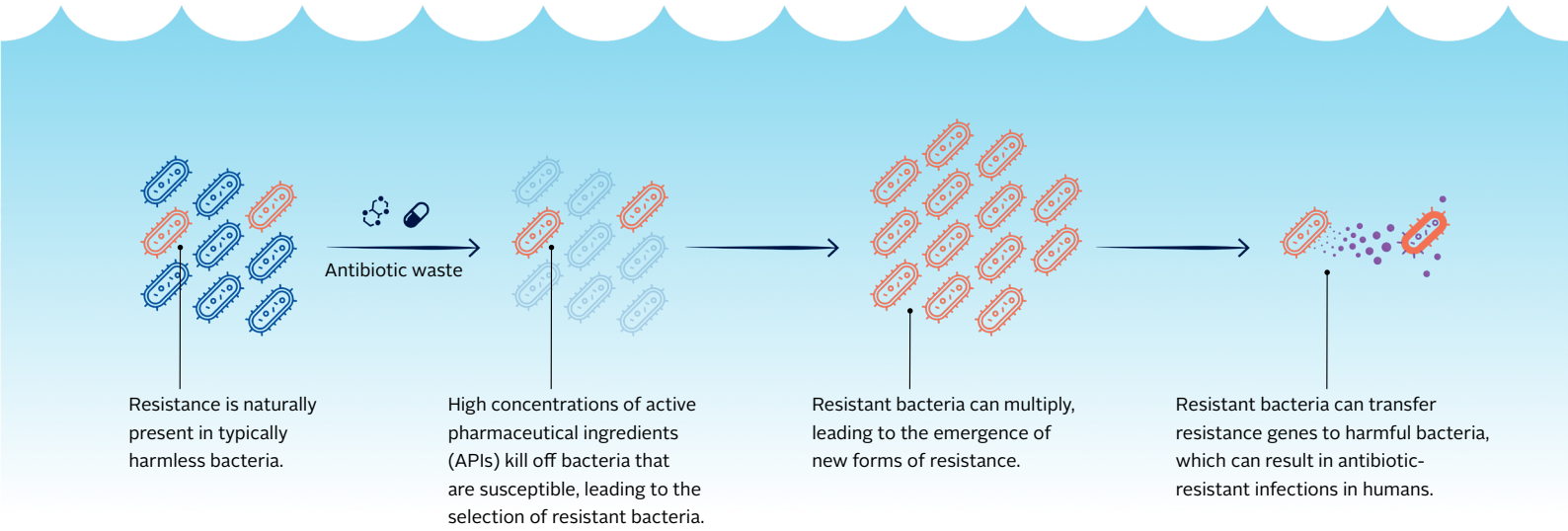
Among the drivers of AMR – which include overuse and misuse of antibiotics, as well as lack of access to appropriate antibiotics – is antibiotic waste that is discharged into the environment during the manufacture of antibiotics.[4,5]

During the manufacturing of antibiotics, large quantities of concentrated waste are generated. While solid waste is typically sent for incineration or to landfill, liquid waste from antibiotic manufacturing is discharged into the environment via receiving waters (i.e., rivers and waterways). When this waste is not properly treated and managed before it is released, high concentrations of active pharmaceutical ingredients (APIs), as well as antibiotic-resistant bacteria and their resistance genes, are discharged into the receiving waters.[6,7] Not only is this potentially harmful to human and animal health, but there is also a serious risk it will contribute to AMR (see Figure 1).[4]

It is therefore critical that companies take responsibility for, and are cautious about, their manufacturing processes. This includes the way in which wastewater is treated before it is released into receiving waters, as well as setting and complying with safe discharge limits on antibiotic waste.

FIGURE 1 **How antibiotic waste can contribute to AMR**

Exposing naturally present and typically harmless bacteria to highly concentrated antibiotics can result in a process known as selective pressure, where the bacteria that are susceptible to the antibiotics present in the wastewater are killed off, leaving the bacteria with evolved resistance genes to survive, multiply and even transfer resistant genes to other bacteria through the process of horizontal gene transfer. As antibiotic resistant genes spread in the environment, they also spread to human and animal populations resulting in antibiotic resistant infections that are hard, or impossible to treat.[8,9]



The pharmaceutical industry's response to the issue

Currently, there are no independently developed global standards or regulations aimed at specifically curtailing antibiotic residues in wastewater to help limit AMR.[10] However, particularly since 2016, multi-organisational approaches have led to the establishment of tools and basic guidance to support pharmaceutical companies in limiting their antibiotic waste from manufacturing.

While these initiatives and platforms are encouraging, it is ultimately up to companies to take voluntary action to limit the release of antibiotic waste into the environment. Importantly, companies can build on the minimum requirements of these guidelines to further develop, implement, and expand their responsible manufacturing practices to limit AMR risk more effectively.

2006

The Pharmaceutical Supply Chain Initiative established

The Pharmaceutical Supply Chain Initiative (PSCI) provides companies with tools to support responsible manufacturing. This industry coalition was formed to establish and promote responsible practices across members' supply chains and, in particular, to make supplier assessments more efficient.

2016

First-ever collaborative response from industry on AMR

The 2016 World Economic Forum (WEF) in Davos marked the first time that the pharmaceutical industry engaged collaboratively to address the rising risks of AMR, including the impact of manufacturing. Following the signing of the "Declaration by the Pharmaceutical, Biotechnology and Diagnostics Industries on Combating Antimicrobial Resistance" by more than 80 companies and associations at WEF, 13 companies signed the "Industry Roadmap for Progress on Combating Antimicrobial Resistance", which set out clear commitments from companies on addressing environmental pollution associated with antibiotic manufacturing.[11,12] This was also a catalyst for the establishment of the AMR Industry Alliance in 2017, which represents a coalition of companies and associations and aims to drive progress on AMR by the life sciences industry.

2018

AMR Industry Alliance publishes Common Antibiotic Manufacturing Framework

In 2018, research-based and generic pharmaceutical companies in the AMR Industry Alliance agreed on a Common Antibiotic Manufacturing Framework, which described a risk-based approach to assessing and controlling antibiotic waste streams from manufacturing.[13] The framework provided a methodology and set of minimum requirements needed to conduct risk evaluations of antibiotic manufacturing sites in the supply chain. In 2022, the AMR Industry Alliance formalised the framework to become the Antibiotic Manufacturing Standard.

2022

AMR Industry Alliance formalises Antibiotic Manufacturing Standard

In the absence of independent regulation targeting the AMR risk from antibiotic manufacturing, the AMR Industry Alliance developed its Antibiotic Manufacturing Standard, facilitated by BSI Standards Limited (BSI).[14] This framework provides guidance and serves as a self-assessment tool for manufacturers in the global antibiotic supply chain to encourage the responsible manufacture of antibiotics. The goal is to minimise both the ecological effects and the risks of AMR in the environment. However, the framework has been subjected to criticism regarding its scientific foundations.[15]

2023

Minimised Risk of AMR Certification Programme launched

In June 2023, BSI launched the global Minimised Risk of Antimicrobial Resistance (AMR) Certification Programme. This certification programme is open to the entire antibiotic supply chain and was initially piloted by several

companies, including Centrient, Pfizer, Roche, Sandoz (100% spin-off from Novartis set for Q4 2023), Teva, and Viatris.[1] The programme includes the third-party verification of production waste streams containing APIs to ensure they are quantified and controlled during manufacturing and meet predicted no-effect concentrations (PNECs) in the receiving environment.

The certification process involves initial conformance evaluation against the Antibiotic Manufacturing Standard of the AMR Industry Alliance and annual surveillance to maintain compliance, leading to a three-year validity to the certificate for that product.[16] Companies holding a valid certificate are responsible for ensuring ongoing effective waste management and reassessing and managing risks in relation to changes in production volumes or waste treatment technologies. While all antibiotic manufacturers are eligible for certification, motivations to participate will depend on factors such as company drivers to minimise antibiotic waste, cost and financial investment drivers, procurers' criteria for rewarding the certification, stakeholder expectations and environmental considerations.

Why actions from pharmaceutical companies can have a significant impact

It is important to note that the pharmaceutical market for manufacturing antibiotics is sprawling and complex, with manufacturing sites worldwide varying in size and capacity. While some sites are large and well-structured, others are smaller and may specialise in manufacturing a single antibiotic. At the same time, supply chains for antibiotics are also highly fragmented, consisting of many players at some stages and very few at other vital stages – with the consequence that there is often a heavy reliance on a limited number of producers of a certain API that is needed to manufacture an antibiotic, for example.[17]

Despite these challenges, the steps pharmaceutical companies take to develop responsible manufacturing practices can have a broader impact across the supply chain.

As a starting point, companies can prioritise responsible manufacturing practices at the manufacturing sites that they operate directly. But pharmaceutical companies are also uniquely positioned to influence and shape the standards of the wide range of third-party suppliers, manufacturers, wholesalers, and retailers they contract across the supply chain. Specifically, they can extend their expectations to suppliers and hold them to account. Where suppliers for a particular API are limited – or a smaller supplier lacks the resources to develop responsible manufacturing practices – pharmaceutical companies can support them.

This report maps out clear actions by a handful of leading companies that are not only taking responsibility at their own manufacturing sites, but also show how they are promoting responsible practices at their suppliers' sites. These examples demonstrate that working towards developing and implementing effective, sustainable manufacturing practices is entirely feasible – and that progress can be made.

How companies can step up to manufacture responsibly

Over the last six years, the Foundation's AMR Benchmark has analysed the manufacturing practices of pharmaceutical companies, finding that while some progress has been made in addressing antibiotic waste released into the environment, significant gaps remain.[18]

To examine the issue more closely, and to identify potential solutions, the findings and analyses in this report zero in on positive examples of what a small number of leading companies are doing to minimise the impact of their antibiotic manufacturing on AMR and the environment.

This report sets out three key areas of focus for companies to drive further progress:

1. **Employ effective methods to reduce AMR risks**
   Firstly, companies need to set and adhere to safe discharge limits and minimise the impacts associated with manufacturing antibiotics. This section sets out the various methods that are best suited to achieving this.

2. **Promote compliance with discharge limits across the supply chain**
   Over and above ensuring compliance with discharge limits at their own manufacturing sites, companies must work with their third-party suppliers to support them in limiting antibiotic waste.

3. **Disclose actions transparently**
   Publicly sharing information on the actions taken by companies and suppliers promotes accountability, allows progress to be tracked, and facilitates further advancements in addressing challenges. Transparent reporting also encourages others to follow suit, fostering ongoing progress.

1. Employ effective methods to reduce AMR risks

When releasing wastewater into the environment, companies need to ensure that the levels of antibiotic concentrations discharged are within safe limits. As identified by the AMR Benchmark, companies generally do this by setting limits based on the predicted no-effect concentrations (PNECs). Companies then comply with their PNEC-based limits to ensure that the levels of antibiotic residue in the environment remain below concentrations that could cause harm to ecosystems and contribute to the development of resistance (see sidebar).

However, companies can go further and employ more robust methods to measure and to apply limits to maximise the effectiveness of their wastewater management.

Considering the latest research in the field, and guidance from experts, there are three key areas companies can address to further mitigate the risk of AMR from manufacturing: a) where to apply limits, b) quantifying antibiotic concentrations and c) waste management strategies for intermediates.

A select few companies have already taken proactive measures in these key areas, setting the example of how companies can do more to ensure the safety of their wastewater.

The importance of differentiating PNEC risk

It is important to note that industry currently assesses for two distinct risks presented by their wastewater: resistance selection and ecological effects in the environment. However, the current approach is to combine these two predicted no-effect concentrations (PNECs) to form a single risk assessment based on the lowest PNEC. Differentiating these risk assessments would provide for a more comprehensive understanding and targeted mitigation of the specific risks involved.

- **Resistance selection risk:** Should compare PNECs with exposure in wastewater.
- **Ecological effects risk:** Should compare PNECs for ecological effects in the recipients of wastewater (such as rivers).

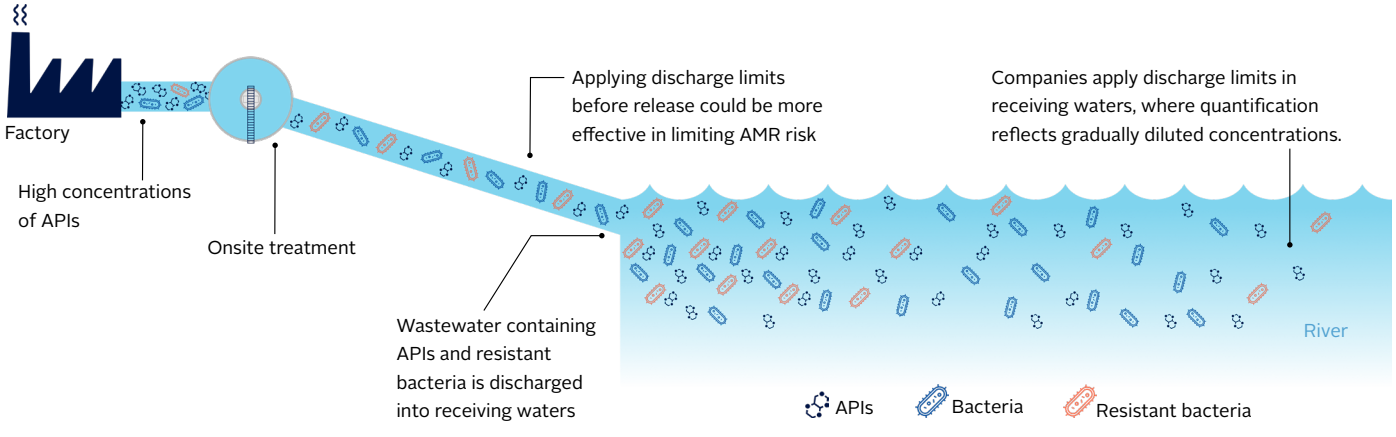
A) Where to apply limits

Among the companies evaluated in the 2021 AMR Benchmark, those that monitor compliance with antibiotic discharge limits typically quantify antibiotic concentrations in the receiving waters. However, it is important to note that this quantification reflects the diluted wastewater. It is, rather, in the undiluted wastewater where bacteria are first exposed to antibiotic waste, including resistance genes already present (see Figure 2).[4]

Additionally, applying discharge limits to antibiotics measured in the receiving waters makes it difficult to determine the proportion of antibiotic waste originating from manufacturing as opposed to other upstream sources, such as hospital effluent or agricultural runoff.

FIGURE 2 **Where to apply limits for antibiotic discharge**

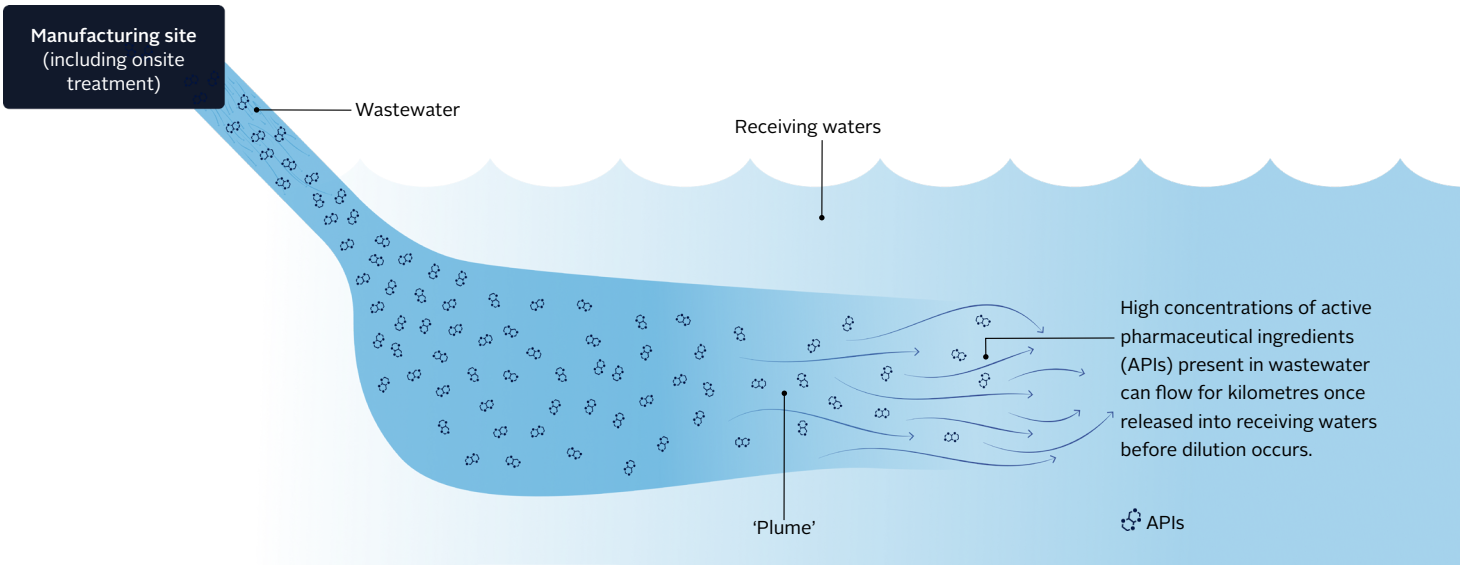
If manufacturers apply antibiotic concentration limits to determine AMR risks, they are set in the receiving waters (e.g., rivers), where the wastewater has already been diluted, rather than directly in the wastewater at the end of pipe. Wastewater is the first point where bacteria are exposed to antibiotic waste and the risk of selection resistance occurs.[4] Once wastewater is discharged into receiving waters, gradual dilution occurs. Applying antibiotic concentration limits in receiving waters may not effectively address the risks associated with resistance selection.



When wastewater is discharged into receiving waters, gradual dilution occurs, which can create a variable "plume" containing APIs that often stretches along prolonged sections of a river, for example (see Figure 3). Dilution in receiving waters can reach high levels (up to several thousandfold), which means that applying PNECs in receiving waters, after dilution has occurred, may not effectively address the risks associated with resistance selection in the undiluted wastewater at a manufacturing site.

FIGURE 3 **Gradual dilution of wastewater can create a variable 'plume'**

As dilution of wastewater can occur slowly once released into receiving waters, it often leads to a prolonged section of a river, for example, where the undiluted wastewater forms a variable 'plume'.



Moreover, a company's wastewater is often sent to a public wastewater treatment plant before being discharged into the environment. Wastewater treatment plants are already recognised as hotspots of resistance selection because they receive wastewater from municipalities, which can contain high levels of bacteria, as well as antibiotic residue from human consumption.[19,20] If wastewater containing high levels of APIs is sent to these same wastewater treatment plants from manufacturing sites, it only poses further risks to the emergence and spread of AMR.

Given the risks associated with only applying discharge limits in receiving waters, it is critical to consider the dilution factors used during the release of wastewater to determine its safety. Since bacterial selective pressure occurs rapidly, within minutes or hours, employing default dilution factors can alleviate the burden of accurately estimating dilution factors for each manufacturing site. However, this approach may result in some degree of over- or underestimation. If the PNEC for resistance selection is directly applied to the wastewater, dilution factors become irrelevant.

Applying discharge limits directly to wastewater can be more effective in reducing AMR risk

By applying discharge limits directly to undiluted wastewater before it is released into receiving waters, companies can minimise AMR more effectively (also see box-out).

If all companies would apply discharge limits directly to undiluted wastewater, it is expected that the risk of accumulating high concentrations will be reduced, particularly in cases where several antibiotic manufacturing sites are located near the same waterway. If a single waterway is exposed to high volumes of antibiotic waste from various sources, the proliferation of resistant bacteria is highly likely, as is the case with the Musi River in India and the Yangtze River Delta in China.[21,22]

Overall, reducing antibiotic concentrations to achieve compliance is challenging and requires resource allocation and access to advanced wastewater treatment technology. Many companies are still striving to achieve compliance with discharge limits in receiving waters – let alone directly in wastewater.

To date, no company assessed in the AMR Benchmark, or in this report, actively reports applying limits directly in its wastewater before releasing it into receiving waters. However, efforts from some companies set encouraging examples of how to mitigate AMR risk in wastewater before it is released into the environment.

EU legislation around emission limits

Applying limits directly to undiluted wastewater aligns with the Industrial Emissions Directive (IED), which is the primary piece of existing legislation in the EU addressing other industrial pollution.

The IED mandates meeting emission limit values at the point of emission (also see p.25 of this report).[23]

Shionogi and Centrient's approaches to ensuring safety of wastewater

Notably, while Shionogi only publicly reports compliance with discharge limits in receiving waters (i.e., after wastewater has been released as guided by the AMR Industry Alliance), in consultations for this report, the company stated that it does comply with discharge limits directly in its wastewater for all five of the antibiotics it manufactures: cefiderocol, flomoxef, latamoxef, doripenem and cefcapene pivoxil*.

To effectively manage antibiotic waste, Shionogi employ's a two-step process at its Kanegasaki and Tokushima sites in Japan, which handle the production of the company's APIs and drug products. Firstly, the antibiotic waste undergoes inactivation through alkaline hydrolysis, followed by biological treatment (see box-out).

Shionogi conducts regular annual monitoring of the antibiotic concentration in actual wastewater from the plants to ensure the safety of its wastewater.[24] The company also conducts monitoring when there is a change in production volume or manufacturing procedure. Moreover, annual supplier audits are carried out to maintain quality control standards. For the proper disposal of solid and sludge waste, Shionogi relies on its external waste contractor, Eco-system Akita Co., Ltd, to incinerate the wastes.

Centrient, a business-to-business provider** of antibiotics and antifungals, implements a comprehensive waste-treatment process to achieve end-of-pipe compliance at its site in Toansa, India.[25,26]

This site, which is responsible for manufacturing semi-synthetic penicillins, is not near any waterways in which treated wastewater can be released. Instead, the site's waste undergoes primary, secondary and tertiary waste-treatment steps before being recycled. The recycled wastewater is repurposed for cooling towers and horticulture. It's important to note that because this recycled wastewater is used for horticulture, it is critical that PNECs are not exceeded.

In 2021, Centrient introduced a wastewater treatment option for specific streams that employs microorganisms without oxygen to degrade organic contaminants found in wastewater. Additionally, solid waste from packaging, which contains traces of intermediates and APIs, undergoes deactivation before being sent to approved recyclers or a controlled landfill.

Limitations of biological wastewater treatment

It is important to note that a limitation in the use of biological wastewater treatments is the reliance on natural organisms, including bacteria, to further breakdown the remaining organic waste. This process increases the risk of exposing bacteria to antibiotics, thereby amplifying the risk of AMR. To mitigate for this risk, it is advisable to test the effluent after treatment.

*Shionogi reports that the actual concentration is below the limit of detection. However, when a worst-case scenario was applied based on the limit of detection, the concentration would exceed the default discharge limit of 0.05 µg/L by only 4,2 ng/L when applied at the end of the pipe. Since such a worst-case scenario likely overestimates the concentration, Shionogi expects that compliance at the end of the pipe is achieved.

**In 2021, Centrient facilitated approximately 1.386 billion patient treatments of penicillins, cephalosporins and nystatin.[25]

Sandoz employs method to remove bacteria from wastewater

Although further research is required to establish the precise correlation between the bacterial quantities in wastewater and resistance selection, it is reasonable to assume that reducing bacterial populations will decrease the AMR risk. Removing bacteria that are present in wastewater before releasing it could thus serve as an additional measure to mitigate the risk of resistance.

For instance, Sandoz, (100% spin-off from Novartis planned Q4 2023) has implemented a membrane filtration process at its primary manufacturing site in Kundl, Austria, to effectively remove bacteria from wastewater effluent.[1,27] The Kundl site specialises in the production of beta-lactams and cephalosporins, covering all production steps from active pharmaceutical ingredients (API) to final drug products.[28]

B) Quantifying antibiotic concentrations

When applying discharge limits, pharmaceutical companies must prioritise the implementation of sensitive detection methods to accurately assess whether these limits are being exceeded. Failing to do so may lead to the release of hazardous concentrations of antibiotics, which can contribute to the selection of resistant bacteria.

The current default approach employed by the companies assessed in this report and in the 2021 AMR Benchmark to determine antibiotic concentrations is the mass balance approach. This method relies on theoretical calculations based on estimated losses during the manufacturing process, as opposed to assessing antibiotic concentrations in wastewater samples.

The mass balance approach does offer a quick and cost-effective way to identify potential hotspots and prioritise actions for improvements. However, it remains unclear whether this method provides the necessary sensitivity to accurately determine if limits are exceeded, particularly if limits are applied to undiluted wastewater. Furthermore, it is less transparent than analyses conducted by third parties, and it does not allow companies to determine the removal efficiency of its wastewater treatments.

The resolution of the mass balance calculations is another important consideration. Specifically, when calculating the average concentrations, companies should focus on the time elapsed after waste – and any potential active antibiotic residue – has been discharged. Calculating over a longer timeframe raises concerns about overlooking peaks characterised by exceptionally high concentrations. For example, critical steps that take place at a manufacturing site that present high risks of discharge for residual antibiotics (such as rinses of reaction tanks) may only take a few minutes, but companies following the guidance of AMR Industry Alliance, for example, may typically calculate the antibiotic concentrations on a daily average.

Abbott, Centrient and Shionogi's strategies to quantify antibiotic concentrations more accurately

In addressing the shortcomings of the mass balance approach, some companies have implemented strategies to assess antibiotic concentrations in wastewater samples as either a complementary method, or as part of a verification step. Company examples include:

- Abbott's pharmaceuticals division utilises a combination of the mass balance approach and wastewater analysis to ensure accurate determination of discharge limits.
- Centrient established a standard practice for its own sites, conducting monthly sampling and quarterly analysis of wastewater samples.
- Shionogi analyses the antibiotic concentration in actual wastewater to verify the safe levels of antibiotics in the wastewater that is discharged into the natural environment.

However, it is important to note that the companies consulted for this report raised concerns regarding the cost and availability of certified laboratories for conducting chemical analysis of wastewater samples in a swift and accurate manner in countries like India, where a lot of antibiotic manufacturing takes place. Drawbacks of sampling also include the retrospective nature and the difficulty in selecting the appropriate moment to collect the sample, thereby risking overlooking discharge peaks.

As demonstrated by Abbott's pharmaceuticals division, companies can achieve more accurate monitoring of antibiotic concentrations in wastewater by implementing a synergistic combination of the mass balance approach and analysis of wastewater samples.

In consultations for this report, companies also highlighted the potential need for tailormade approaches to achieve accurate measurements. When quantifying antibiotic concentrations in wastewater, for example, they can employ different methods at the various manufacturing sites in their supply chains, depending on the nature of the manufacturing operation and the type of antibiotic that is being manufactured.

C) Waste management strategies for intermediates

Antibiotic intermediates are the precursor molecules used in the manufacturing of antibiotics, and some intermediates can possess pharmaceutical activity, including antibacterial properties. However, it is important to note that not all intermediates exhibit the same spectrum of activity or potency as the final antibiotic product. Additionally, not all antibiotics are synthesised using intermediates with antibiotic activity. That said, the significant volume of waste generated during the production of intermediates compared to APIs and finished drug products is a concern.[29,30]

There is currently a lack of industry guidance on intermediates and among the companies covered in this report and the 2021 AMR Benchmark, only Centrient has taken proactive steps to establish discharge limits for intermediates. Centrient monitors compliance with discharge limits at relevant manufacturing sites, for 6-APA and 7-ADCA.

Notably, 6-APA,7-ACA and 7-ADCA (see box-out) are intermediates well-known for having antimicrobial activity.[29,31] While the exact contribution of an intermediate's waste to AMR is not clearly defined, it is important for companies and their suppliers, who predominately produce the intermediates, to take a cautious approach and include intermediates into their environmental risk management strategies.

Examples of intermediates with antimicrobial activity [29,31]

6-APA: intermediate used in the production of penicillin derivatives such as amoxicillin and ampicillin.

7-ACA and 7-ADCA: intermediates used in the production of cephalosporins like ceftriaxone and cefuroxime.

RECOMMENDATIONS FOR COMPANIES

- Set discharge limits and apply these limits directly in the wastewater that leaves the manufacturing site.
- Set up long-term plans that aim to support supply chain compliance, including the setting of discharge limits and where to apply them.
- Be transparent on concentrations of antibiotics in wastewater; if a company only applies limits to the recipient, it must be transparent about the dilution factors employed.
- Combine the mass balance approach with sampling and chemical analysis to assess antibiotic concentrations in wastewater as accurately as possible.
- Set limits and reach compliance for intermediates with known antimicrobial activity.

2. Promote compliance with discharge limits across the supply chain

In employing effective methods to ensure antibiotic discharge stays below safe limits, companies also need to ensure compliance with these limits to mitigate the development of AMR, protect human health, and preserve the effectiveness of antibiotics. As a starting point, companies need to strive to achieve compliance at their own manufacturing sites, following which they can hold suppliers to the same standards.

Ensuring compliance at own manufacturing sites

Recent assessments of companies within the scope of the AMR Benchmark reports indicate that more pharmaceutical companies are now ensuring compliance at their own manufacturing sites. In 2021, the AMR Benchmark assessed the compliance of 187 sites directly operated by pharmaceutical companies and found that 97 reported to be in accordance with discharge limits that they set.[18]

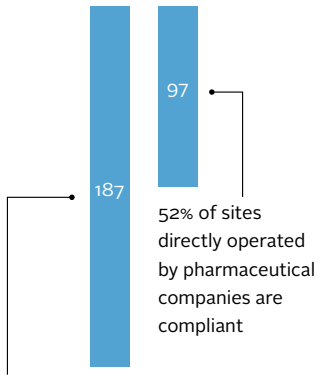
This report identifies that, to date, only five companies – namely Aurobindo, Centrient*, GSK, Shionogi and Viatris – report that all their manufacturing sites comply with discharge limits set for the receiving environment.

Viatris and GSK highlighted that key measures they employ to achieve compliance include practices such as dry vacuum cleaning, pre-rinsing of manufacturing equipment and collecting these concentrated streams at the point of generation to send for appropriate disposal, such as incineration.

Notably, Centrient reports achieving compliance by implementing advanced wastewater treatment facilities at its sites. At one site, an effluent stream posed challenges due to detectable residual antibiotics and high levels of inorganic salts, making conventional treatment methods ineffective. To address this issue, Centrient's bioprocessing laboratory devised a solution based on biocatalysis, without the use of bacteria, to eliminate the residual antibiotics.

These approaches demonstrate how companies that have achieved compliance across all their manufacturing sites have taken progressive steps to achieve this. Reaching full compliance at all sites operated by a company 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 to successfully implement them.

Over half of sites directly operated by pharmaceutical companies are reported to be in accordance with discharge limits in the receiving environment



Sites directly operated by pharmaceutical companies analysed by the AMR Benchmark, including 93 operated by large research-based pharmaceutical companies and 94 operated by generic medicine manufacturers.

Source: 2021 AMR Benchmark

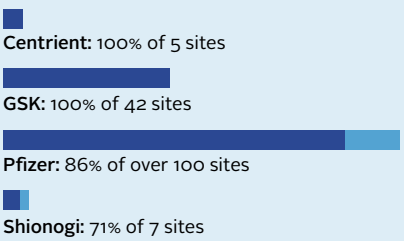
Supporting supplier compliance with discharge limits and providing assistance to address challenges

By taking responsibility not only for themselves but also across their supply chain, companies can address waste management practices in a more comprehensive and holistic manner, and effectively reduce the risks associated with the release of antibiotic waste.

As identified over the three iterations of the AMR Benchmark reports, pharmaceutical companies have made progress on applying the discharge limits at third-party supplier sites (suppliers). Where gaps still exist, companies can consider various approaches – as highlighted by the company examples in this report – to increase supplier compliance.

Notably, Centrient, GSK, Pfizer and Shionogi report that the majority of their supplier sites are compliant (see box-out). While Centrient and Shionogi do have a smaller number of supplier sites, GSK and Pfizer demonstrate that achieving compliance on a larger scale is also possible.

Leading companies report significant supplier compliance with discharge limits



*Reaching compliance at the in 2021 acquired Astral SteriTech site is still in progress and expected end of 2023.

To support their suppliers, companies need to raise awareness of AMR, communicate the risks of waste produced by the manufacture of antibiotics, and provide training so that suppliers can enhance their practices to manufacture more responsibly. The companies consulted for this report highlighted that they often provide the necessary tools and provide support to suppliers through membership of the Pharmaceutical Supply Chain Initiative (PSCI).

However, despite such support, there can be significant challenges in achieving compliance, particularly for smaller suppliers who may lack sufficient resources or expertise. For example, in some cases, yield improvements and proper cleaning processes may not be sufficient to meet discharge limits. Wastewater treatment technologies may be required, which, if expensive, can pose financial challenges for small manufacturers operating with slim profit margins.

Where such resources are required, collaboration between companies and public and/or private partners can help with solutions, as envisioned by an initiative to establish the AMR Centre of Excellence (CoE) in Hyderabad, India. The CoE, with planned funding contributions from the Indian government and pharmaceutical companies such as Dr Reddys, has been conceptualised and developed by the Responsible Antibiotics Manufacturing Platform (RAMP)* (see sidebar).

The CoE offers an opportunity for companies to assist their suppliers in adopting responsible waste practices, while reducing the financial burden associated with it. This collaborative initiative is intended to provide the support required to accelerate compliance with discharge limits throughout the entire supply chain.

While joining forces with other stakeholders will help accelerate progress in curbing AMR from manufacturing, companies must be proactive in taking steps to facilitate this, as demonstrated by an initiative undertaken by Abbott, a generic medicine manufacturer:

AMR Centre of Excellence in India

In collaboration with local regulators, academic research institutes and pharmaceutical companies, the Centre of Excellence (CoE), planned to be based in Hyderabad, India, will support manufacturers in achieving sustainable antibiotic manufacturing.[33] The CoE is focused on four key objectives:

1. Provide training and awareness to professionals – including environmental, health and safety (EHS) staff and procurers – about AMR, responsible manufacturing and industry best practices.
2. Build capacity for monitoring technologies and affordable testing solutions to ensure manufacturers can analyse wastewater samples.
3. Provide a testbed for treatment technologies to showcase solutions that reduce antibiotic discharges at lower costs.
4. Support policy research and advocacy in the development of AMR action plans, national guidelines, and advisory services on academic, operational and policy issues.

Abbott supports suppliers with free wastewater analysis and logistics assistance

Analysing antibiotic waste concentrations where PNECs are as low as tens of nanograms per litre, requires the appropriate skills and experience. To assist its suppliers with this, Abbott's pharmaceuticals division has established a partnership with a specialised laboratory to develop testing methods for its molecules. Since 2022, Abbott has been offering free analysis of wastewater samples to all supplier sites that exceed limits from the mass balance approach. By facilitating testing and covering costs, Abbott aims to support its contracted manufacturing suppliers in conducting water analysis more efficiently.

Additionally, Abbott aids suppliers in addressing any logistical issues that may arise in the process. The free testing service offered by Abbott also covers any necessary follow-up tests needed during remedial actions.

By offering this service, Abbott aims to ensure its contracted suppliers adopt sustainable environmental practices and foster long-term relationships. Within PSCI, a team member of Abbott in India is leading a working group dedicated to increasing the number of certified laboratories capable of analysing wastewater samples in the country.

Finding certified laboratories that can perform swift and accurate chemical analyses of wastewater samples is a challenge faced worldwide. Abbott's approach demonstrates how companies can take the initiative to help address this. If more companies follow suit in supporting suppliers, this could have a significant impact on building a sustainable supply chain of responsible players.

*The AMR Centre of Excellence project was recommended and developed by the Responsible Antibiotics Manufacturing Platform (RAMP) project. RAMP is a collaborative platform which engages with stakeholders to encourage more sustainably produced antibiotics and to promote coherence between the voluntary action of companies, government policies and regulations, standards and market incentives.[32]

Including contractual provisions to promote suppliers' AMR risk management

Pharmaceutical companies can elevate standards at supplier sites by incorporating contractual provisions that mandate compliance with discharge limits. When these provisions are uniformly implemented, suppliers are incentivised to meet the new standards and implement best practices. Where suppliers are non-compliant, pharmaceutical companies can hold them accountable by enforcing contracts and seeking alternative suppliers.

However, it must be noted that replacing a supplier may be a challenge or have significant consequences for supply chain management, especially where there are limited suppliers of a critical drug (see box-out). As a result, companies avoid enforcing manufacturing standards for high-risk molecules to maintain supply chain stability. To ensure a reliable supply of antibiotics, particularly for products where dependency on a limited number of suppliers exists, companies generally prefer to prioritise long-term partnerships and support suppliers in achieving compliance.

Prior to the AMR Benchmark 2021, no company reported the inclusion of AMR-related risk management in its supplier contracts. However, among the companies included in this report, Abbott, Centrient*, GSK, Sandoz, Shionogi and Pfizer have introduced contractual provisions to address this issue. These provisions encompass practices for managing liquid and solid waste, compliance with discharge limits, and the provision of discharge level information. Through audits, these companies assess supplier conformance with the established contracts.

Pfizer demonstrates a clear approach to how it holds third-party suppliers to its own company standards.

Limited suppliers for critical drugs

In January 2023, a global shortage of amoxicillin was reported amid a surge of respiratory infections that drove an increase in demand for antibiotics. The European Medicines Agency noted that this shortage was compounded by manufacturing delays and production capacity issues.[34]

Amoxicillin is one of the most widely used broad-spectrum antibiotics (Browne 2021). While around 17 manufacturing sites produce the API, only seven sites worldwide manufacture the intermediate 6-APA, with five of them located in China.[29]

Pfizer enforces supplier contracts to uphold manufacturing standards

Pfizer has evaluated its antibiotic wastewater concentrations against discharge limits at over 100 supplier sites, reporting compliance at 86% of those. Pfizer is working with the remainder as part of its strategy to help suppliers achieve published PNECs by the end of 2025.[35] The company has dedicated staff in place to engage suppliers and support the implementation of risk management based on the guidance of the AMR Industry Alliance's Antibiotic Manufacturing Standard.

Pfizer conducts supplier site visits to offer support and assist with calculating mass balances while also ensuring that suppliers are abiding by contractual provisions with Pfizer. These contractual provisions include following the Alliance's guidance and complying with discharge limits in the recipient (e.g., in a river or waterway) to reduce AMR risk.

Pfizer reports that it has terminated the contracts of seven suppliers since 2021 that it identified as not meeting the company's expectations in terms of environmental, health and safety (EHS) performance. While these supplier contract terminations were not specifically due to AMR-related risks, they do demonstrate that Pfizer actively enforces contracts based on its EHS standards.

GSK develops contractual provisions with suppliers and replaces wastewater treatment company

GSK's contractual provisions include compliance with discharge limits for third-party suppliers; they are currently being integrated into existing contracts and will be a standard requirement for future contracts. To date, GSK has not found it necessary to enforce contractual requirements to address non-compliance with the discharge limits among our suppliers.

However, GSK did take action – although not explicitly intended to address AMR-related risks – when a privately-owned wastewater treatment plant it contracted with was not upholding GSK standards. A GSK manufacturing site in the Middle East previously sent its discharge (downstream of onsite controls) to a third-party private wastewater treatment company that employed ultimate evaporation of wastewater, with disposal of residual sludge via landfill. As this treatment

*Centrient has not been assessed in the three iterations of the Foundation's AMR Benchmark.

technology was not compliant with GSK standards, its manufacturing site shifted its discharge to an alternative private wastewater-treatment company that employs multiple treatment technologies to fully recycle the treated wastewater and incinerate any residual sludge, thereby likely minimising the risk of AMR.

RECOMMENDATIONS FOR COMPANIES

- Create awareness among suppliers on AMR risk from manufacturing.
- Ensure that suppliers set and comply with discharge limits.
- Actively share knowledge and expertise with suppliers to support them in achieving compliance with discharge limits.
- Share resources and analytical capability with suppliers, such as testing of wastewater, free of charge.
- Include provisions and set expectations on managing AMR risk in new and existing supplier contracts.
- If suppliers are non-compliant with provisions in their contracts to prevent AMR risk, enforce contract terminations. This recommendation depends on the availability of alternative suppliers with demonstrated commitments to responsible manufacturing.

3. Disclose actions transparently

When companies take action to mitigate AMR risks through responsible manufacturing, it is critical that they provide clear information about the initiatives and processes that are being implemented at their own manufacturing sites, and how they are monitoring supplier compliance. Not only will this allow for accountability across the supply chain, but it can offer much-needed insights into the relationship between wastewater management and AMR.

Why disclosing details on manufacturing practices is important

It is good practice for companies to publish audit results from their own sites, as well as from audits conducted at supplier sites, including actual discharge levels, monitoring methods and dilution factors used (if any). This information can help stakeholders (such as experts in the field) to study the relationship between wastewater management and AMR.

Moreover, providing clear information about waste management practices, including mass balance calculations and dilution factors, will facilitate the independent evaluation of a company's performance. This has clear benefits in terms of responsible procurement. When such detailed disclosure is made public, procurers can assess the AMR risks associated with a company's manufacturing practices and make informed purchasing decisions (see p.25). For example, when procuring antibiotics, governments and hospitals can also use this information to ensure these medicines have been produced to standard.[36]

Public disclosure of the names and locations (city or district) of their manufacturing sites and those of their suppliers can also facilitate the identification of potential hotspots and risk areas for AMR and local environmental pollution. This can enable independent third parties, such as global health organisations, academic experts, and government institutions, to better understand the global health impact of antibiotic manufacturing. Greater transparency across the complex and fragile antibiotic supply chain also supports governments in identifying pressure points, allowing them to anticipate shortages and implementing appropriate mitigation measures.[36]

Very few companies publicly disclose information on responsible manufacturing practices

To date, the AMR Benchmark has found that companies fall short on transparency when it comes to disclosing information on how they address AMR through their manufacturing practices. None of the 17 companies evaluated in the 2020 Benchmark reported publishing audit results or the identities of third-party suppliers, for example. The 2021 Benchmark identified that very few companies publicly report on the number of manufacturing sites audited, or on compliance with safe levels.

Companies also do not publicly disclose the actual levels of antibiotic residue entering local soil and water. This is in line with observed findings in the animal pharmaceutical sector identified by FAIRR, an investor network that raises awareness on environmental, social and governance (ESG) risks in the agriculture and food value chains. FAIRR's research, including an assessment of seven major animal pharmaceutical companies' actions to address AMR, revealed that none of them currently disclose information on how antibiotic waste within their supply chains is managed.[37]

Some of the companies in scope of the Benchmark reports cite confidentiality and contractual agreements and restrictions as reasons for not publicly disclosing such information. Competitive concerns and risks to credibility have also been indicated as factors that discourage disclosure.

Five companies assessed in this report – Centrient, GSK, Shionogi, Teva and Viatris – do, however, publicly report on their waste management practices (see table below). While they disclose different degrees of information, these companies are taking steps in the right direction and demonstrate that it is possible for companies to make details of their practices public.

Shionogi, in particular, serves as an example of how a company can provide clarity on its responsible manufacturing practices across its antibacterial manufacturing supply chain. Notably, the company discloses the country-level location of each of its suppliers and the name of its external waste-management treatment plant.

However, none of these companies, or any of the others assessed by the AMR Benchmark, report on the actual levels of antibacterial residue entering local soil and water, or the dilution factors applied, and no company publishes its audit results. Until companies provide more clarity, it will remain difficult to truly assess risks to the environment and the spread of AMR – and to hold companies accountable.

Companies that publicly disclose their waste management practices

Company	Compliance	Location
Shionogi serves as a positive example of a company that provides clarity on its antibacterial manufacturing supply chain.[24]	Shares the names of the antibacterials in its portfolio and maps the manufacturing of these products to its own sites and suppliers' sites, reporting the level of compliance with PNECs for each.	Discloses location of suppliers at country level (Japan, Italy and India). Discloses name of external waste-treatment plant (Eco-system Akita Co., Ltd)
Centrient publicly discloses details on how it manages the AMR risk of its antibiotics and antifungals from manufacturing.	Provides detail on methods and technologies and how it collaborates with suppliers. Published a white paper setting out how it reaches PNEC compliance in the full supply chain.[28]	Publicly discloses the exact locations of each of its manufacturing sites for the products it produces and on compliance to PNEC.[25]
Teva publicly reports on the compliance of its own sites with discharge limits, and that it is taking remedial action when discharge limits are exceeded.	In its 2022 ESG Report, Teva indicated that it successfully achieved its target of assessing 100% of the 33 Teva sites that handle antimicrobial drug substances and products in 2021. Teva also reported 20 sites discharge to be below PNEC. For sites with at least one antibiotic above PNEC, Teva indicated it provided technical support aimed at reducing discharges – including the implementation of corrective and preventive actions to address findings and ensure proper governance and oversight.[39]	
GSK publicly shares summaries of some of its environmental risk assessments on its website, such as summaries for amoxicillin and cefuroxime.[40]	In its 2022 ESG Report, GSK indicated that 100% of its own sites and 98% of its supplier sites achieved compliance with PNECs.[41]	
Viatris publicly discloses details on its progress in limiting AMR via responsible manufacturing	Viatris reports, in its Sustainability Report 2022, that all manufacturing sites with antibiotic manufacturing are compliant with PNECs, as calculated by mass balance. In addition, it is disclosed that Viatris carried out 15 supplier risk assessments in 2022 to assess adherence with the Antibiotic Manufacturing Standard with non-compliant suppliers developing and implementing corrective actions.[42]	

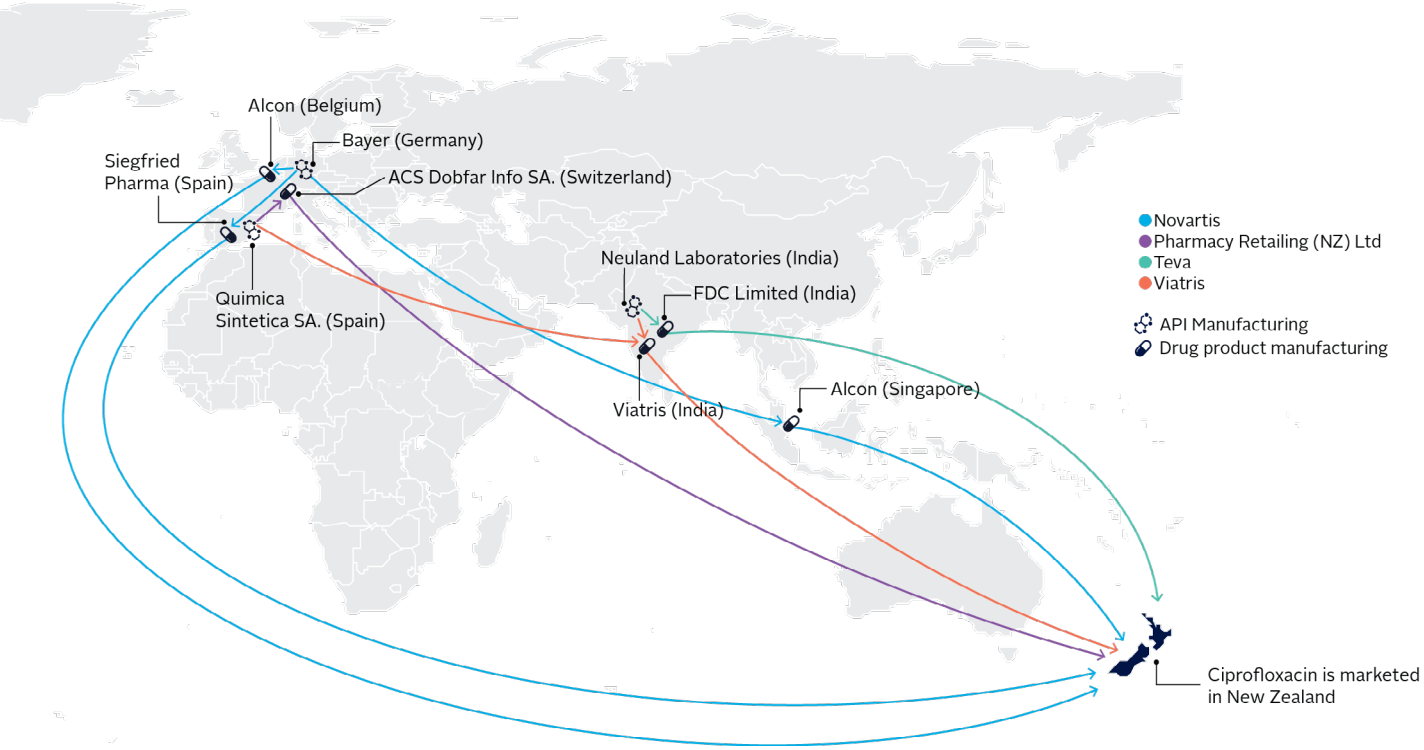
New Zealand example demonstrates that public disclosure of supply chains by companies is feasible

The New Zealand Medicines and Medical Devices Safety Authority mandates public disclosure from companies in their supply chains (see Figure 4).[43] Information on the full supply chain of each marketed product in New Zealand is collated in a publicly available database and includes details on the manufacturing, packaging, and release of products, the suppliers (including names and locations) that supply each active ingredient, as well as the product sponsors.

This transparent approach enables New Zealand's government and other stakeholders to identify supply chain bottlenecks and anticipate potential shortages. Additionally, the public availability of this information enables the government to gain better insights into potential sources and locations of pollution within the supply chain and enables procurers to prioritise the procurement of antibiotics that have been manufactured without contributing to AMR.[6,7,44]

FIGURE 4 **Public disclosure on global supply chains shows where potential AMR risks from manufacturing are located - New Zealand case study on ciprofloxacin**

This map shows the global supply chains for all actively marketed formulations of ciprofloxacin in New Zealand. Ciprofloxacin is a commonly prescribed antibiotic in the treatment of Gram-negative bacterial infections associated with urinary, respiratory, and gastrointestinal infections. Being chemically synthesised, ciprofloxacin is relatively stable compared to other antibiotics and difficult to degrade. Consequently, ciprofloxacin is frequently detected in high concentrations in the environment, raising concerns about its impact on AMR.[6,7,44]



RECOMMENDATIONS FOR COMPANIES

- Publicly disclose audit results, including discharge levels and dilution factors. Existing collaborative platforms, such as the AMR Industry Alliance or the PSCI, can also be used to coordinate public disclosure of audit results.
- Companies can renegotiate contracts to facilitate the publication of results of supplier audits.
- Disclose the manufacturer and location for each manufacturing step in the supply chain.
- Report on AMR risk from manufacturing in requests and questionnaires from ESG data providers and rating agencies.

Why is responsible manufacturing becoming an operational and business priority for companies?

Manufacturing antibiotics responsibly is not only a moral imperative, but it is also a critical operational and business priority, particularly in the pharmaceutical industry.

Antibiotics are essential healthcare products that directly impact patient health and safety. By maintaining high standards for manufacturing and waste management, companies can protect the environment, safeguard public health and ensure the long-term availability of effective antibiotics.

The benefits of responsible manufacturing overwhelmingly outweigh the perceived challenges. For example, responsible and sustainable manufacturing and waste management practices can:

- Support quality assurance;
- Mitigate risks to public health and the environment;
- Ensure adherence to regulations;
- Align with corporate social responsibilities; and
- Enhance a company's reputation, leading to increased trust and business opportunities.

Since 2016, AMR risk from manufacturing has gained increasing attention – with international action resulting in notable progress over the last few years. Additionally, the World Health Organization (WHO) is currently in the process of developing an independent guidance on waste and wastewater management for antibiotic manufacturing (see sidebar).

In line with this global focus, several stakeholders – including governments, regulators, procurers, global health organisations and investors – are increasingly expecting responsible manufacturing practices from pharmaceutical companies.

Procurers, for example, who can consider criteria related to the environment and sustainability when making purchasing decisions, are increasingly expecting companies to demonstrate comprehensive and effective practices to limit antibiotic waste. More investors also now view AMR as a systemic risk that needs to be considered within environmental, social and governance (ESG) standard-setting and reporting frameworks. There are also signs that regulation aimed at reducing AMR risk from manufacturing, which is currently lacking, may be introduced, or strengthened, in several countries.

The examples set out in this section of the report demonstrate why companies should be proactive in developing and implementing responsible manufacturing practices. By acting now and investing in responsible manufacturing, companies will not only help minimise the propagation of AMR, but can set themselves apart in the market. Moreover, by building a reputation for quality and reliability, companies are setting a foundation for long-term success.

The World Health Organization is developing guidance for pharmaceutical manufacturing. To address the environmental dimension of AMR resulting from the pharmaceutical production of antibacterials, the World Health Organization (WHO) is in the process of developing an independent guidance on waste and wastewater management in pharmaceutical manufacturing with a focus on antimicrobials.

This document – of which the release date is to be determined – will use good manufacturing practice (GMP) risk management principles and the water safety framework common across all WHO water safety guidance as a point of departure.

STAYING AHEAD OF EVOLVING REGULATIONS

At present, there is a lack of internationally agreed actions or measures to control or limit the release of antimicrobials and antimicrobial resistant bacteria and genes (ARB/ARGs) into the environment. However, some governing bodies and governments are taking steps to control antibiotic residue levels in the environment, and have introduced incentives to encourage responsible manufacturing practices by companies.

European Union

The EU has identified AMR as one of the top three health threats that its constituent countries are facing.[45] Accordingly, in April 2023, the European Commission proposed new and more stringent legislation. Under this proposal, pharmaceutical companies seeking to market their medicines in the EU are required to conduct an environmental risk assessment (ERA) of medicines to evaluate the potential adverse impacts of medicines on the environment and public health. This includes the risk of AMR from the manufacturing of antibiotics. Failure to comply may now lead to the refusal of marketing authorisation. This legislative change will require companies to implement measures, such as proper disposal protocols and wastewater treatment to limit the impact of their products.[46]

Furthermore, the Extended Producer Responsibility scheme under the Urban Wastewater Directive makes pharmaceutical producers financially responsible for the removal of pharmaceuticals, including antibiotics, by public wastewater treatment plants. This shift aligns with the principle of "polluter pays" and highlights the industry's role in keeping water clean of pharmaceutical residues.[47]

Additionally, indirect measures are in place to address industrial pollution. The Industrial Emissions Directive (IED) mandates compliance with emissions limit values, ensuring companies adhere to specified thresholds. The Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) legislation establishes specific dilution factors for discharging substances into water bodies, further safeguarding the environment.[23]

These changes, currently considered by the European Parliament and the Council in the standard legislative procedure, are intended to combat AMR, protect the environment, and promote responsible pharmaceutical manufacturing and waste management practices in the EU.

China and India

Antibacterial production involves numerous manufacturing sites worldwide, with a high proportion of them based in China and India. China accounted for more than 40% of global antibiotics exports by value in 2021.[48] In both countries, concerns around rising AMR and its impact on the environment are gaining increased attention.

In China, the government has implemented a range of strategies to combat AMR and reduce environmental and safety risks. In 2018, tax legislation was introduced to incentivise high polluting industries, including the pharmaceutical industry, to adopt more sustainable practices.[49] However, it is important to note that, as yet, this legislation does not target the discharge of active pharmaceutical ingredients (APIs) during antibiotic manufacturing.

China's National Action Plan on AMR (NAP) 2022-2025 recognises the environmental impact of AMR and includes measures to strengthen control over antimicrobial pollution discharge and to monitor antimicrobials in water environments.[50] In 2021, China issued the "Notice on the Reform Implementation Plan for Hazardous Waste Management Supervision and Utilization Capacity" to improve the management and supervision of hazardous wastes. This hazardous waste list includes solid waste from antibiotics, indicating regulations for managing some pharmaceutical waste.[51]

India is increasingly prioritising responsible manufacturing practices and placing more emphasis on requirements for companies. All API bulk-drug manufacturing sites are classified as "grossly polluting industries" and are required to adhere to zero liquid discharge (ZLD) standards.[52] For example, Abbott reports that the use of ZLD technology is mandated by Himachal Pradesh's Pollution Control Board (PCB). This state's PCB has started collecting monthly wastewater samples at manufacturing sites to analyse antimicrobial residues and found that a third of monitored antibiotic manufacturers were exceeding discharge limits.[53]

With India holding the 2023 G20 presidency, the G20 Summit taking place in the country in September 2023 provides an opportunity for countries to call for further actions from pharmaceutical companies to limit AMR.

To further reinforce the implementation of existing regulations, the National Green Tribunal (NGT), a specialised federal body dealing with environmental protection, is taking assertive measures where there is adverse impact on public health and environment due to non-compliance.[54] In an attempt to put regulation in place, the Indian government proposed legislation in 2019 that included discharge limits on antibiotics in wastewater discharged from manufacturing sites into receiving waterways.[55] Although the final published legislation in 2021 did not include such discharge limits, the NGT has ordered its implementation in an ongoing legal case.[56]

As China and India increase oversight and tightening of regulations, companies would be well-served to proactively prioritise responsible manufacturing practices and measures in these manufacturing hubs.

MEETING GROWING STAKEHOLDER EXPECTATIONS

Some countries, regional bodies and organisations have taken leading steps to improve responsible manufacturing. While some of these examples showcase growing expectations from procurers in high-income countries, oftentimes they will procure antibiotics that are manufactured in low- and middle-income countries (LMICs), such as China and India. As a result, procurement decisions can have an impact on responsible manufacturing practices in these countries.

However, going forward, greater global harmonisation and the adoption of similar practices in countries across the globe will need to be prioritised in order to have a substantial global impact on responsible manufacturing (see sidebar).

RAMP Framework guides stakeholders with harmonised manufacturing criteria

In July 2023, the Responsible Antibiotics Manufacturing Platform (RAMP) published a framework that provides a set of guidelines and independent criteria to evaluate and verify a company's manufacturing practices in reducing the risks of antimicrobial resistance (AMR).[52] The framework harmonises existing criteria by industry, academia, procurers and regulators and makes these accessible for voluntary implementation. This aims to spur cross-sectoral collaboration between stakeholders and provides them the opportunity to adopt similar practices that go beyond the current voluntary commitments of pharmaceutical companies.

Norway's sustainable procurement pilot

The Norwegian Hospital Procurement Agency initiated a sustainable procurement pilot in 2019, covering all anti-infectives necessary in Norwegian hospitals. The pilot included non-price tender criteria, promoting the procurement of the best possible product, rather than the cheapest. The criteria focused on environmental considerations, security of supply and other product characteristics that were considered important by healthcare professionals. The environmental considerations – weighted at 30% of the allocation criteria – specifically addressed whether companies have environmentally friendly production in place and reduce the risk of AMR.[57]

After years of decreasing competition, the programme resulted in a significant increase in the number of companies submitting tender offers, thereby enabling more competition. Notably, three companies in the scope of this report – Fresenius Kabi, Sandoz (100% spin-off from Novartis planned Q4 2023) and Viatris – were awarded with tenders partly for achieving the highest score on environmental criteria compared with other participating companies (see Figure 5). These companies demonstrate that embracing responsible manufacturing practices helped to position them favourably in the market.

FIGURE 5 **Three companies in scope awarded with tenders due to responsible manufacturing**

As part of the Norwegian Hospital Procurement Agency's 2019 sustainable procurement pilot, three companies in scope of this report were awarded with tenders, partly for achieving the highest score on environmental criteria that specifically addressed whether companies have environmentally friendly production in place and reduce the risk of AMR.

Company	Product
Fresenius Kabi	Ceftazidime Ceftriaxone Cefuroxime Linezolid (infusion)
Sandoz*	Linezolid (tablet)
Viatris	Clindamycin Cloxacillin

*Sandoz is the generics division of Novartis (100% spin-off planned Q4 2023).

The success of the pilot has led to plans to optimise and streamline the criteria for the most critical aspects of AMR risk reduction. Going forward, more stringent requirements regarding compliance with discharge limits across the supply chain, as well as transparency, will be implemented. For example, competing companies will need to disclose the names and locations of suppliers, which will help the Norwegian government to better reward companies that engage in responsible manufacturing across the supply chain. This will also provide the necessary clarity to ensure that tender-winning companies do not only depend on one supplier to produce the API (also see “Disclose actions transparently” on p.21-23).

Sweden’s AMR risk criteria in procurement

In Sweden, AMR risk criteria are integrated into regional tenders for hospital procurement. Although the adoption of environmental criteria by the 21 Swedish regions is not mandatory, there has been a notable upswing in their implementation. For example, in the densely populated region of Västra Götaland, environmental criteria now account for approximately 25% of the tender while the number of companies participating in the tenders remained constant.

Additionally, the Swedish Medical Products Agency, Dental and Pharmaceutical Benefits Agency, and E-Health Agency are collaborating to pilot, between 2025 and 2028, the implementation of an environmental premium for antibiotics sold in pharmacies. The stringent criteria of the proposed premium will only consider companies that comply with PNECs directly in wastewater, rather than in the receiving waters (also see “Employ effective methods to reduce AMR risks” on p.11-16).[58]

UK’s NHS Commitment to responsible antimicrobial procurement

In the UK, the National Health Service (NHS) emphasises responsible antimicrobial procurement through contracts that promote good stewardship, manufacturing, and environmental practices; monitor for emerging resistance; and ensure a reliable supply. Informed by the AMR Benchmark Report of the Access to Medicine Foundation – the NHS has set up evaluation criteria that manufacturers must meet to qualify for a procurement contract. The evaluation criteria are equally applicable to contract requirements of the recently introduced delinked and subscription-based contracts for two antibiotics: Shionogi’s cefiderocol and Pfizer’s ceftazidime/avibactam.[59]

The NHS mandates companies’ adherence to good antimicrobial manufacturing practices and environmental standards throughout the supply chain – at the company’s own and/or its suppliers’ manufacturing sites, as well as its external wastewater treatment plants – including compliance with discharge limits (also see "Promote compliance with discharge limits across the supply chain" on p.17-20).[60,61] Additionally, the NHS requires companies to be signatories of the AMR Industry Alliance Declaration and comply with the AMR Industry Alliance antibiotic manufacturing standard.

Health insurer AOK demonstrates how other stakeholders can promote responsible manufacturing

AOK, a German health insurer, has incorporated criteria related to PNEC compliance in tendering processes to promote and reward responsible manufacturing.[25] AOK’s inclusion of PNEC criteria underscores another key stakeholder, in this case a health insurer, promoting responsible manufacturing in response to, among other things, the economic implications of AMR.

GARDP’s selection of responsible manufacturers

The Global AMR Research & Development Partnership (GARDP) selects manufacturers for its sublicense agreements based on their commitment to meeting high standards in areas such as environmental sustainability, quality assurance and responsible production.

GARDP was granted the right to develop, manufacture, and commercialise the antibiotic cefiderocol through sub-licensees in 135 countries. When selecting a manufacturer, GARDP, with the support of Clinton Health Access Initiative (CHAI), incorporated environmental criteria into its Request for Proposals (RFP), particularly focusing on waste management practices to limit AMR. This included a requirement for the manufacturer to have the ability to reach compliance with discharge limits (also see" Employ effective methods to reduce AMR risks" on p.11-16).[62]

To ensure the selected manufacturer (the name of the manufacturer has not yet been disclosed) adheres to these criteria, GARDP has conducted an intensive audit of the manufacturer's practices, including evaluations of Good Manufacturing Practices (GMP), financial aspects, and Environmental Health and Safety (EHS) measures. In addition, a stipulation on compliance with discharge limits is included in the draft sublicence contract with the manufacturer. By integrating the environmental criteria and conducting thorough audits, GARDP strives to ensure that the manufacturer adheres to stringent environmental standards.

Investors are expecting action on AMR

In efforts to help curb AMR, and to mitigate the systemic risks it poses from a business perspective, investors are working to formally integrate AMR risks as part of their decision making – with the launch of the Investor Action on AMR initiative in 2020 serving as an example. This coalition between the Access to Medicine Foundation, the FAIRR initiative, the Principles for Responsible Investment and the UK Government of Health and Social Care seeks to galvanise investor efforts to address AMR globally.[63] With investors focusing on this issue, their expectations of pharmaceutical companies will increase – and transparency and accountability around their manufacturing practices, for instance, will become crucial.

By including responsible manufacturing practices as part of their environmental, social and governance (ESG) strategies, companies can respond to investors' existing sustainability expectations, as well as proactively meet future interest from investors.

For example, Amundi, a major asset manager in France, is actively engaging with leading ESG data providers and standard setters to include AMR metrics in company evaluations and standards. Notably, Institutional Shareholder Services (ISS), an ESG corporate rating provider, has already integrated metrics on environmental risk management strategies related to AMR risks and publicly discloses its findings.[64] This trend further emphasises the importance of companies disclosing their AMR risk management efforts and committing to responsible manufacturing.

SEIZING BUSINESS OPPORTUNITIES AS AFRICAN UNION PROMOTES LOCAL MANUFACTURING

People living in sub-Saharan Africa face a high mortality rate due to AMR.[3] Local production is a critical step for several reasons, including ensuring reliable supply, promoting health security, reducing costs over the long term, improving regulatory oversight, and driving economic growth. Initiatives like the Pharmaceutical Manufacturing Plan for Africa (PMPA) by the African Union and Africa CDC are actively promoting increased local manufacturing. This can present an immense opportunity for growth on the continent, particularly if companies embrace robust and responsible manufacturing practices from the outset.

In many African countries, wastewater is often used in the production of drinking water and beverages, with the consequences of inadequately treated wastewater extending beyond the contamination of the receiving environment.[8,65-67] By prioritising responsible manufacturing, companies can also contribute to socioeconomic development by addressing issues such as inadequate effluent treatment, poorly designed wastewater treatment plants, and water contamination.

Going forward

Collaborative efforts are vital in addressing the risks posed by pharmaceutical manufacturing. However, as demonstrated by some of the global trends around AMR and the environment, companies will need to take proactive action of their own accord. Those that take responsibility for their manufacturing practices will ensure their compliance with regulators, governments and procurers can make a substantial impact on curbing AMR and safeguarding the environment, while enjoying growth, sustainability and a positive reputation.

Staying ahead of the curve

Addressing the global health and environmental risks posed by antimicrobial resistance (AMR) will require unwavering commitment and decisive action. To help curb this global health threat, pharmaceutical companies must acknowledge the impact of their manufacturing practices and take measures to manage antibiotic waste across the manufacturing supply chain.

This report has mapped out clear actions by a handful of leading companies that are already working towards developing and implementing manufacturing practices that are effective and sustainable – showing that progress is entirely possible. Looking to these standout examples, and by focusing on the areas of action set out in this report, more companies can adopt responsible manufacturing practices to reduce AMR risk.

IN BRIEF

- Poor waste management in the manufacturing of antibiotics contributes to AMR.
- Pharmaceutical companies occupy a central position in the antibiotic manufacturing supply chain and need to do more to limit antibiotic waste, starting at their own manufacturing sites.
- Developing long-term, close relationships with suppliers can promote responsible manufacturing across the supply chain, which can lead to a substantial impact.
- By being transparent about the actions they are taking to reduce AMR risk from manufacturing, companies can proactively meet future expectations from stakeholders.
- Positive examples from companies in scope of this report show that it is entirely possible to go further in developing responsible manufacturing practices to more effectively limit antibiotic waste to help curb AMR.

Methods matter

While employing the tools provided by the AMR Industry Alliance and the Pharmaceutical supply Chain Initiative (PSCI) is certainly a positive step, especially since doing this is entirely voluntary, companies can go beyond the guidance these tools provide.

Specifically, to minimise AMR risk more effectively, companies can develop and implement comprehensive methods to ensure the safety of their wastewater before it is released into the environment.

Companies can apply discharge limits directly to their wastewater, instead of applying limits before releasing it into the environment. Notably, in consultations for this report, Shionogi stated that it complies with discharge limits directly in its wastewater for all five of the antibiotics it manufactures. If more companies were to strive to achieve this for more products, the risk of AMR from manufacturing waste would be significantly reduced.

To more accurately determine whether discharge limits are being met, companies can implement a synergistic combination of the mass balance approach and analysis of wastewater samples, as demonstrated by Abbott.

Companies can also be proactive in further limiting AMR risk in their wastewater by removing bacteria from it. Sandoz (100% spin-off from Novartis planned Q4 2023) does this at its main antibiotic manufacturing site in Kundl, Austria, through a membrane filtration process.

In developing their waste management practices, companies can consider intermediates – the precursor molecules used in the manufacturing of antibiotics. While the link between an intermediate's waste and AMR is not clearly defined, companies and their suppliers need to take a cautious approach. Currently, only Centrient has taken proactive steps to establish discharge limits for intermediates. The company monitors compliance with discharge limits at relevant manufacturing sites for the intermediates 6-APA and 7-ADCA, both well-known for having antimicrobial activity.[29,31]

As demonstrated by these examples, companies can take practical steps to limit AMR risks in their wastewater at their own manufacturing sites as effectively as possible. However, it is important to note that companies will need to tailor their approaches to consider, for example, the nature of the manufacturing operation, the type of antibiotic that is being manufactured, as well as the resources and costs involved.

Compliance with discharge limits across the supply chain is key

Beyond employing effective methods at their own manufacturing sites to ensure discharge limits are compliant with safe levels, Centrient, GSK, Pfizer and Shionogi, have also been able to achieve compliance at the majority of their supplier sites.

By leveraging their central position in the supply chain, companies can hold their third-party suppliers to account and support them where needed. Collaborative approaches that combine incentives and contractual provisions have shown promise in improving compliance along the supply chain. As demonstrated by GSK and Pfizer, companies can include provisions and set expectations on managing AMR risk in new and existing supplier contracts.

If a supplier is non-compliant and needs to be replaced, companies can ensure they consult and engage alternative suppliers with demonstrated commitment to responsible manufacturing. However, the fragility of the supply chain – especially the fact that for some critical drugs, there are only a few producers – cannot be ignored. Replacing a supplier may be a challenge or have significant consequences for supply chain management and access to antibiotics. For this reason, companies avoid enforcing manufacturing standards for high-risk molecules. Instead, as noted in this report, companies generally prefer to build long-term partnerships with suppliers to ensure a reliable supply of antibiotics, particularly for products where dependency on a limited number of suppliers exists.

With this in mind, companies can create awareness among their suppliers on AMR risk from manufacturing and actively share knowledge, resources, expertise and analytical capabilities to support them in achieving compliance with discharge limits. As demonstrated by Abbott, providing suppliers with wastewater sample analysis, free of charge, is a practical way of doing this. Specifically, where smaller suppliers lack resources, providing them with such tangible support is critical to ensuring sustainability of a responsible manufacturing supply chain.

Taking transparent, proactive action to ensure sustainability

It is one thing to engage in efforts to manage waste, but without public disclosure there is no way to hold companies accountable or to tap into the practices that are yielding positive results.

By providing information about their methods (such as how they quantify concentrations) and compliance (including actual discharge levels), companies allow for accountability and offer much-needed insights into the relationship between wastewater management and AMR.

While Shionogi leads the way in providing clarity across its antibacterial supply chain, no company assessed in the AMR Benchmark, or this report, provides details of actual discharge levels – even though disclosing such information is straightforward. Apart from Shionogi, only Centrient, GSK, Teva and Viatris disclose more specific details about their manufacturing practices.

Over and above the need for accountability that transparency affords, global health stakeholders are looking to companies that demonstrate a commitment to sustainability – including through their manufacturing practices. Procurers, for example, who can consider criteria related to the environment and sustainability when making purchasing decisions, are increasingly expecting companies to demonstrate comprehensive and effective practices to limit antibiotic waste. By being clear about their efforts to manufacture responsibly, companies can position themselves favourably within the market.

Notably, three companies in scope of this report – Fresenius Kabi, Sandoz and Viatris – were awarded with tenders as part of the Norwegian Hospital Procurement Agency's 2019 sustainable pilot procurement programme. The companies received the tenders partly for achieving the highest score on environmental criteria, which specifically considered whether companies had environmentally friendly production in place to reduce the risk of AMR.

By following the recommendations included in this report and integrating robust responsible manufacturing practices into their business operations, companies can ensure they drive meaningful progress in addressing AMR while proactively preparing to meet growing expectations.

Contributing to a sustainable future

The antibiotic manufacturing supply chain is complex and includes a wide range of players, but actions from pharmaceutical companies are especially vital in moving the needle. While collective initiatives within the pharmaceutical industry are encouraging, individual companies need to make sure they play their part and continually work towards strengthening and improving their practices. As set out in this report, there are companies that are already proactively and voluntarily strengthening their AMR mitigation efforts. More companies now need to seize opportunities for progress by ensuring they develop and scale responsible manufacturing practices – and extend expectations to suppliers.

Inaction will not only be detrimental to the fight against AMR, but can have consequences for companies that are not at the forefront of a global health landscape that is focusing on the drivers that fuel drug resistance – including antibiotic waste from manufacturing.

DEFINITIONS

- **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.

- **Antibacterial medicine**: 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 antibiotics

- **Antibiotics:** Equivalent to Antibacterial medicine. The term "antibiotic" is often used inconsistently in literature to denote either a drug that targets any type of microorganism in the body or, alternatively, a drug that targets bacteria specifically

- **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.

- **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.

- **End of pipe:** An approach to pollution control which concentrates upon effluent treatment or filtration prior to discharge into the environment via receiving waters, as opposed to making changes in the process giving rise to the wastes.

- **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.

- **Mass Balance Approach:** A method used to estimate the amount of antibacterial ingredients lost during the production process that subsequently could be present in waste. It consists of estimating the how much of the antibacterial ingredient is lost in the production process and will end up in waste, i.e., the mass balance, applying the removal efficiency of antibacterial residue through on-site treatment and other treatment plants and applying dilution factors resulting from water flows from treatment plants and rivers. This approach allows companies to estimate the final concentration of antibacterials in the receiving environment without directly measuring them in the wastewater samples.

- **Pharmaceutical Supply Chain Initiative (PSCI):** Pharmaceutical Supply Chain Initiative is a membership body driving action for safety, environmental, and social outcomes across the global pharma & healthcare supply chain.

- **Predicted No Effect Concentration (PNEC):** i.e., the highest estimated concentration at which no effects of concern are expected to occur in an ecosystem, such as the opportunity for resistance selection or harm to aquatic life. Typically referred to as discharge limits.

- **Recipient:** The receiving environment in which antibiotic waste from manufacturing sites is discharged into. Typically, this includes waterways such as rivers, streams, lakes and oceans.

- **Selection Pressure:** The influence exerted by some factor (such as an antibiotic) on natural selection to promote one group of organisms over another. In the case of antibiotic resistance, antibiotics cause a selective pressure by killing susceptible bacteria, allowing antibiotic-resistant bacteria to survive, develop and multiply.

- **Wastewater:** Wastewater or liquid waste that may contain antibiotic residues and is released from manufacturing facilities, hospitals, or other sources where antibiotics may be used or produced. Wastewater is often referred to as effluent and is considered safe when PNECs are met (see PNEC).

- **Zero liquid discharge (ZLD) technology:** This 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. (Ranade 2014)

REFERENCES

1 Novartis raises 2023 forecast, maps out Sandoz spin-off | Reuters. Accessed July 20, 2023. https://www.reuters.com/business/healthcare-pharmaceuticals/novartis-raises-full-year-outlook-launches-new-share-buyback-scheme-2023-07-18/

2 WHO. Ten threats to global health in 2019. Accessed January 18, 2023. https://www.who.int/news-room/spotlight/ten-threats-to-global-health-in-2019

3 Murray CJ, Ikuta KS, Sharara F, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet. 2022;399(10325):629-655. doi:10.1016/S0140-6736(21)02724-0

4 Larsson J, Flach C-F. Antibiotic resistance in the environment. Nat Rev Microbiol. 2022;20(5):257-269. doi:10.1038/s41579-021-00649-x

5 UNEP. Bracing for Superbugs: Strengthening Environmental Action in the One Health Response to Antimicrobial Resistance | UNEP - UN Environment Programme.; 2023. Accessed February 7, 2023. https://www.unep.org/resources/superbugs/environmental-action

6 Booth A, Aga DS, Wester AL. Retrospective analysis of the global antibiotic residues that exceed the predicted no effect concentration for antimicrobial resistance in various environmental matrices. Environ Int. 2020;141:105796. doi:10.1016/j.envint.2020.105796

7 Wilkinson JL, Boxall ABA, Kolpin DW, et al. Pharmaceutical pollution of the world's rivers. Proc Natl Acad Sci U S A. 2022;119(8). doi:10.1073/PNAS.2113947119

8 Mutuku C, Gazdag Z, Melegh S. Occurrence of antibiotics and bacterial resistance genes in wastewater: resistance mechanisms and antimicrobial resistance control approaches. World J Microbiol Biotechnol. 2022;38(9):1-27. doi:10.1007/s11274-022-03334-0

9 Baym M, Stone LK, Kishony R. Multidrug evolutionary strategies to reverse antibiotic resistance. Science (80-). 2016;351(6268). doi:10.1126/science.aad3292

10 Miettinen M, Khan SA. Pharmaceutical pollution: A weakly regulated global environmental risk. Rev Eur Comp Int Environ Law. 2022;31(1):75-88. doi:10.1111/reel.12422

11 Davos. Declaration by the Pharmaceutical, Biotechnology and Diagnostics Industries on Combating Antimicrobial Resistance.; 2016.

12 AMR Industry Alliance. Industry Roadmap for Progress on Combating Antimicrobial Resistance. Published online 2016:3 p. Accessed May 26, 2023. https://www.amrindustryalliance.org/industry-roadmap-for-progress-on-combating-antimicrobial-resistance/

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

14 AMR Industry Alliance. AMR Industry Alliance Launches Antibiotic Manufacturing Standard to Help Mitigate the Impacts of Antimicrobial Resistance - AMR Industry Alliance. Accessed January 16, 2023. https://www.amrindustryalliance.org/mediaroom/amr-industry-alliance-launches-antibiotic-manufacturing-standard-to-help-mitigate-the-impacts-of-antimicrobial-resistance/

15 Larsson J. "The industry sets standards for emissions on its own terms" - LäkemedelsVärlden.https://www.lakemedelsvarlden.se/antibiotikaindustrins-egen-utslappsstandard-pa-deras-villkor/. Published June 14, 2022. Accessed January 16, 2023.

16 BSI Group. New certification facilitated by BSI for the AMR Industry Alliance | BSI. Accessed July 20, 2023. https://www.bsigroup.com/en-GB/about-bsi/media-centre/press-releases/2023/june/new-certification-aims-to-mitigate-antimicrobial-resistance-risk-in-antibiotic-manufacturing/

17 Access to Medicine Foundation. Shortages, stockouts and scarcity: the issues facing the security of antibiotic supply and the role for pharmaceutical companies. Amsterdam. Published May 31, 2018. Accessed March 31, 2022. https://accesstomedicinefoundation.org/publications/shortages-stock-outs-and-scarcity-the-issues-facing-the-security-of-antibiotic-supply-and-the-role-for-pharmaceutical-companies

18 Access to Medicine Foundation. Progress on limiting release of antibiotic waste into environment, but gaps remain. Accessed July 20, 2023. https://accesstomedicinefoundation.org/resource/progress-on-limiting-release-of-antibiotic-waste-into-environment-but-gaps-remain

19 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

20 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

21 Gothwal R, Thatikonda S. Role of environmental pollution in prevalence of antibiotic resistant bacteria in aquatic environment of river: case of Musi river, South India. Water Environ J. 2017;31(4):456-462. doi:10.1111/WEJ.12263

22 Wu Q, Li Y, Wu Y, Li F, Zhong S. The spatial spillover effect of environmental regulation on the total factor productivity of pharmaceutical manufacturing industry in China. Sci Rep. 2022;12(1). doi:10.1038/s41598-022-15614-8

23 Council of the European Union. Proposal for a Directive of the European Parliament and of the Council amending Directive 2010/75/EU of the European Parliament and of the Council of 24 November 2010 on industrial emissions. Published 2023. https://data.consilium.europa.eu/doc/document/ST-7310-2023-INIT/en/pdf

24 Shionogi. Environmental Report 2022. Published online 2023. https://www.shionogi.com/content/dam/shionogi/global/investors/ir-library/annual-report-integrated-report/pdf/environment Report_2022_e.pdf

25 Centrient. ESG Report 2021. Published online 2022:1-117.

26 Centrient. Centrient's Toansa Manufacturing Site in India Leads the Way in Wastewater Management. Accessed May 26, 2023. https://www.centrient.com/media/centrients-toansa-manufacturing-site-in-dia-leads-way-wastewater-management

27 Novartis. Sustainability Report 2022 for Novartis Austria. Published 2022. https://www.sandoz.at/sites/www.sandoz.at/files/2022_Nachhaltigkeitsbericht2022_ENG_FINAL.pdf

28 Sandoz. Anti-Infectives. Accessed May 24, 2023. https://www.sandoz.com/products-services/disease-areas/anti-infectives

29 Boston Consulting Group and Wellcome Trust. Understanding the Antibiotic Manufacturing Ecosystem: A View of Global Supply Chains, Pressure Points, and Implications for Antimicrobial Resistance Response.; 2022. Accessed May 26, 2023. https://cms.wellcome.org/sites/default/files/2022-04/understanding-the-antibiotic-manufacturing-ecosystem-2022.pdf

30 Han Z, Feng H, Luan X, et al. Three-Year Consecutive Field Application of Erythromycin Fermentation Residue Following Hydrothermal Treatment: Cumulative Effect on Soil Antibiotic Resistance Genes. Engineering. 2022;15:78-88. doi:10.1016/j.eng.2022.05.011

31 Sawant AM, Sunder AV, Vamkudoth KR, Ramasamy S, Pundle A. Process Development for 6-Aminopenicillanic Acid Production Using Lentikats-Encapsulated Escherichia coli Cells Expressing Penicillin v Acylase. ACS Omega. 2020;5(45):28972-28976. doi:10.1021/ACSOMEGA.0C02813/SUPPL_FILE/AO0C02813_SI_001.PDF

32 Stockholm International Water Institute (SIWI). Responsible Antibiotics Manufacturing Platform (RAMP). Accessed July 24, 2023. https://siwi.org/amr-ramp/

33 SIWI. Webinar: Sustainable Antibiotic Manufacturing Practices in India - YouTube. Published 2022. Accessed July 24, 2023. https://www.youtube.com/watch?v=32yLoamKvbg&t=3936s

34 EMA update on shortages of antibiotics in the EU | European Medicines Agency. Accessed July 24, 2023. https://www.ema.europa.eu/en/news/ema-update-shortages-antibiotics-eu

35 CDP Water Security 2022 - Pfizer. Accessed July 24, 2023. https://www.cdp.net/en/responses?per_page=10&queries%5Bname%5D=pfizer&sort_by=project_year&sort_dir=-desc

36 Årdal C, Baraldi E, Beyer P, et al. Supply chain transparency and the availability of essential medicines. Bull World Health Organ. 2021;99(4):319-320. doi:10.2471/BLT.20.267724

37 FAIRR. Antimicrobial Resistance and Antibiotic Stewardship in the Animal Pharmaceutical Industry Animal Pharmaceuticals Engagement 2022 / 23. 2023;(May).

38 Centrient. Manufacturing sustainable antibiotics for the future Achieving a PNEC-compliant supply chain Reaching our goal of a clean antibiotics supply chain. Published online 2022.

39 Teva. ESG Progress Report 2022.; 2022. https://www.tevapharm.com/our-impact/esg-progress-report/

40 GSK - ERA List. Accessed July 24, 2023. https://www.msds-gsk.com/ERAList.aspx

41 GSK. ESG Perfomance Report 2022. Published online 2022.

42 Viatris. Sustainability Report 2022. Published online 2022.

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

44 Hanna N, Tamhankar AJ, Lundborg CS. The development of an integrated environment–human risk approach for the prioritisation of antibiotics for policy decisions. Sci Total Environ. 2023;880:163301. doi:10.1016/J.SCITOTENV.2023.163301

45 European Commission. EU Action on Antimicrobial Resistance.

46 A pharmaceutical strategy for Europe. Accessed July 24, 2023. https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe_en

47 European Commission. DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL concerning urban wastewater treatment. 2022;0345.

48 China Dominates the Antibiotics Market | Statista. Published 2022. Accessed July 24, 2023. https://www.statista.com/chart/27709/distribution-of-global-antibiotics-export-value-by-country/

49 The Impact of China's Environmental Law on the Procurement of API and Excipients. Published 2019. Accessed January 5, 2023. https://www.beroeinc.com/whitepaper/the-impact-chinas-environmental-law-on-procurement-of-api-and-excipients/

50 National Health Commission of the People's Republic of China. National Action Plan to Contain Antimicrobial Resistance (2022-2025). Accessed January 5, 2023. http://www.nhc.gov.cn/yzygj/s7659/202210/2875ad7e2b2e46a2a672240ed9ee750f.shtml

51 Zhang Y, Walsh TR, Wang Y, Shen J, Yang M. Minimizing Risks of

Antimicrobial Resistance Development in the Environment from a Public One Health Perspective. China CDC Wkly. 2022;4(49):1105-1109. doi:10.46234/ccdcw2022.224

52 Panorel I., Schaaf N., Verma, N., Shaw B., Salin, K. and Prakash S. 2023. Responsible Antibiotics Manufacturing Platform (RAMP) Framework, Stockholm International Water Institute.

53 Antibiotic residue in river, 37 Himachal Pradesh firms in dock : The Tribune India. Accessed July 11, 2023. https://www.tribuneindia.com/news/himachal/antibiotic-residue-in-river-37-himachal-pradesh-firms-in-dock-370468

54 National Green Tribunal. Accessed July 24, 2023. https://www.greentribunal.gov.in/methodology-ngt

55 CIDRAP-ASP Report The Limit of Limits: India's Hurdles in Regulating Antimicrobial Pollution.

56 National Green Tribunal. Case No. 136/2020 ENVIRONMENT (PROTECTION) ACT, 1986. Published 2022. https://green-tribunal.gov.in/caseDetails/DELHI/07011020085820 20

57 Norwegian Hospital Procurement Trust (Sykehusinnkjøp HF). Experience Report – Environmental Requirements for Pharmaceutical Procurements 2020-2022. Accessed February 16, 2023. www.sykehusinnkjop.no

58 Swedish Medical Products Agency. Trial operation for an environmental premium in the benefits system Interim report (Miljöpremie och försäkringsskydd i läkemedelsförmånerna). 2022;04129. www.tlv.se

59 National Institute for Health and Care Excellence (NICE). Models for the evaluation and purchase of antimicrobials. Accessed April 17, 2023. https://www.nice.org.uk/about/what-we-do/life-sciences/scientific-advice/models-for-the-evaluation-and-purchase-of-antimicrobials

60 NHS England. Annex 1 : Selection Questionnaire (SQ) Evaluation Criteria (new antimicrobials). Published online 2020:1-16.

61 NHS England. Annex 3: Award questions and criteria. Published online 2021. https://www.nice.org.uk/Media/Default/About/what-we-do/Life-sciences/award-questions-criteria-annex3.pdf

62 GARDP, CHAI, Shionogi. Request for Proposal for Cefiderocol Access and Stewardship Project. :1-24.

63 IAAMR. Investor Action on Antimicrobial Resistance Investor efforts , achievements and opportunities ahead. Published online 2022.

64 ISS. The Looming Antimicrobial Resistance (AMR) Pandemic: Implications For Investors. Accessed April 4, 2023. https://insights.issgovernance.com/posts/the-looming-antimicrobial-resistance-amr-pandemic-implications-for-investors/

65 Angiro C, Abila PPO, Omara T. Effects of industrial effluents on the quality of water in Namanve stream, Kampala Industrial and Business Park, Uganda. BMC Res Notes. 2020;13(1):1-6. doi:10.1186/S13104-020-05061-X/FIGURES/2

66 Nantaba F, Wasswa J, Kylin H, Palm WU, Bouwman H, Kümmerer K. Occurrence, distribution, and ecotoxicological risk assessment of selected pharmaceutical compounds in water from Lake Victoria, Uganda. Chemosphere. 2020;239:124642. doi:10.1016/J.CHEMOSPHERE.2019.124642

67 Ogunbanwo OM, Kay P, Boxall AB, et al. High Concentrations of Pharmaceuticals in a Nigerian River Catchment. Environ Toxicol Chem. 2022;41(3):551-558. doi:10.1002/ETC.4879

Report Design
Tomas Alexander

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.

Access to Medicine Foundation
Naritaweg 227A
1043 CB Amsterdam
The Netherlands

www.accesstomedicinefoundation.org
info@accesstomedicinefoundation.org
+31 (0)20 21 53 535