

Making antibiotics responsibly

A common manufacturing framework
to tackle antimicrobial resistance



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About this booklet

Representing more than 100 biotech, diagnostics, generics and research-based pharmaceutical companies and associations, the AMR Industry Alliance is one of the largest private sector coalitions working to help find sustainable solutions to antimicrobial resistance (AMR).

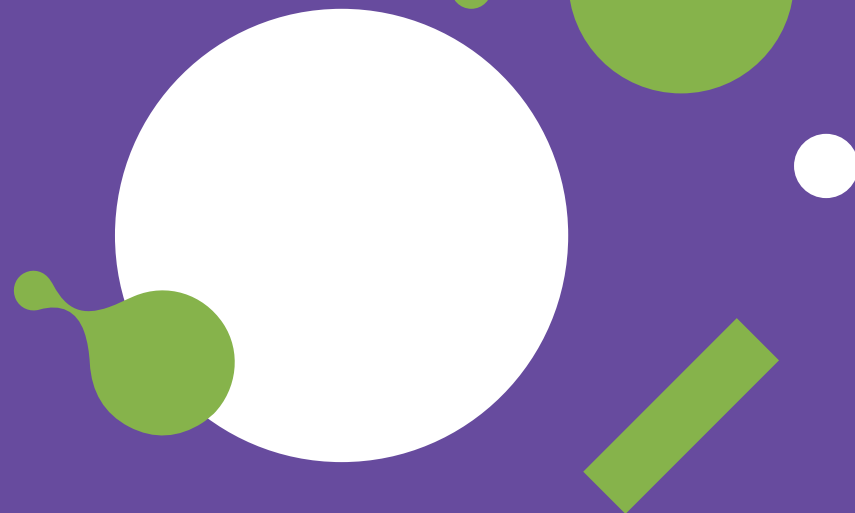
All our members take actions appropriate to the nature of their business to address AMR risk.

The solution we present here is **a common framework for responsible antibiotic manufacturing**. The framework sets out our minimum expectations for business policies, practices and behaviors to minimize the release of antibiotics into the environment from drug production and formulation. With a focus on effective waste management and control, the framework is designed to minimize conditions that may increase the development and spread of resistant bacteria.

Around a fifth of our members¹ supply antibiotics and all of these are committed to implementing the manufacturing framework, both in their own operations and in those of their suppliers.

¹ The AMR Industry Alliance comprises companies and trade associations. Of our member companies, around 20% supply commercial antibiotics to the market. Other members include diagnostic companies and biotech companies (typically engaged in early reach and development of potential new antibiotics).

01 Introduction



A global phenomenon

Antibiotics are used to prevent and treat bacterial infections. Antibiotic resistance happens when bacteria evolve to withstand the effects of antibiotics, making infections harder to treat. It is a naturally occurring phenomenon that has existed for millions of years.

But the overuse and misuse of antibiotics is rapidly accelerating the pace at which resistance develops and spreads.

Antibiotic resistance has reached alarming levels all over the world. More resistance means higher medical costs, longer hospital stays and more deaths from infection.

Around 700,000 people already die from drug-resistant infections every year. But this figure is rising fast and experts warn it could reach ten million a year by 2050. [1]

In a drug-resistant world, many medical interventions that rely on antibiotics to ward off infection—including cancer chemotherapy, organ transplants and even caesarean sections or hip replacements—will also become much riskier.

The loss of effective antibiotics to treat sick animals and plants would similarly compromise food security. In low-income countries, resistant infections in livestock can strip poor households of their main economic asset, destroying the livelihoods of those that can least afford to lose them. The World Bank estimates that by 2030, AMR (including antibiotic resistance) could force up to 24 million people into extreme poverty. [2]

At a global level, unchecked antimicrobial resistance is expected to be as costly as the 2008–2009 financial crisis, shrinking annual global GDP by trillions of dollars every year by 2030. [2]

Alliance action

In 2016, the UN called on countries, companies and civil society to take broad, coordinated action to address the root causes of AMR, which span multiple sectors including human and animal health, pharmaceuticals, food and agriculture, finance, environment and development.

The AMR Industry Alliance is the life sciences industry's response to that call for action. We are one of the largest private sector coalitions set up to help find sustainable solutions to curb AMR. Our members are committed to keeping antibiotics effective and promoting innovation by contributing to, and measuring their efforts in, four key areas: research, appropriate use, access and responsible manufacturing. [3]

This booklet focuses on our fourth area of work and the role of manufacturing in reducing the potential environmental risk arising from antibiotic production and formulation.

Antibiotic resistance happens when bacteria evolve to withstand the effects of antibiotics, making infections harder to treat.

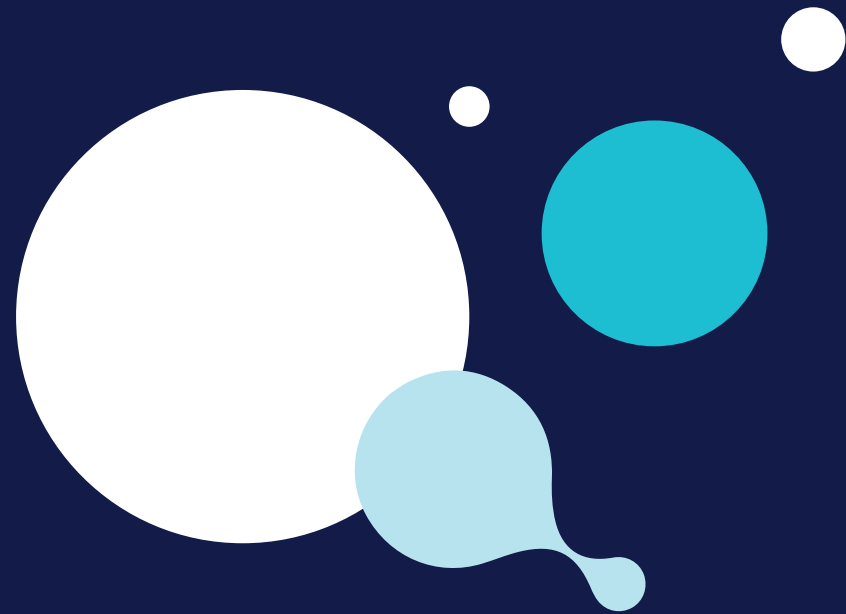
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There are many drivers behind antimicrobial resistance, from poor infection control, lack of awareness and misdiagnoses to over-prescription, falsified drugs and the presence of antibiotics in the environment.



02

The challenge



Sources of resistance

Without human activity, selection for resistance happens naturally as environmental bacteria in soil, water and other habitats constantly evolve to survive and succeed. But overuse and misuse of antimicrobial drugs (including antibiotics) in human medicine and food production is rapidly accelerating the pace at which AMR develops and

spreads. By taking the wrong kind of drug, not completing a course of treatment, or using low concentrations of antibiotics (either unintentionally through poor quality medicines, or on purpose to promote growth in animals), patients, prescribers and food producers are helping microbes to develop resistance the world over.

There are many factors at play, from poor infection control, lack of awareness and misdiagnoses to over-prescription, falsified drugs and rising levels of antibiotics in the environment.

Active residues of antibiotics and resistant bacteria can find their way into the environment in four key ways (see Figure 1):



Human and animal use and excretion by people and animals (pets, horses and food animals) **using antibiotics is by far the biggest source of antibiotics in the environment.** [4] Untreated sewage discharges from densely populated areas can include high levels of antibiotics. But even treated waste can be a problem: municipal wastewater treatment plants, for example, are rarely designed to remove antibiotics.



Agricultural applications, including using manure or biosolids as a fertilizer and the administration of antibiotics in aquaculture, **are acknowledged as poorly understood yet potentially significant sources of environmental contamination.** [5] For example, in aquaculture, up to 75% of the antibiotics used in fish feed may be lost into the surrounding environment. [4]



Inappropriate disposal of used or expired drugs is another, albeit much smaller, **source of environmental contamination.**

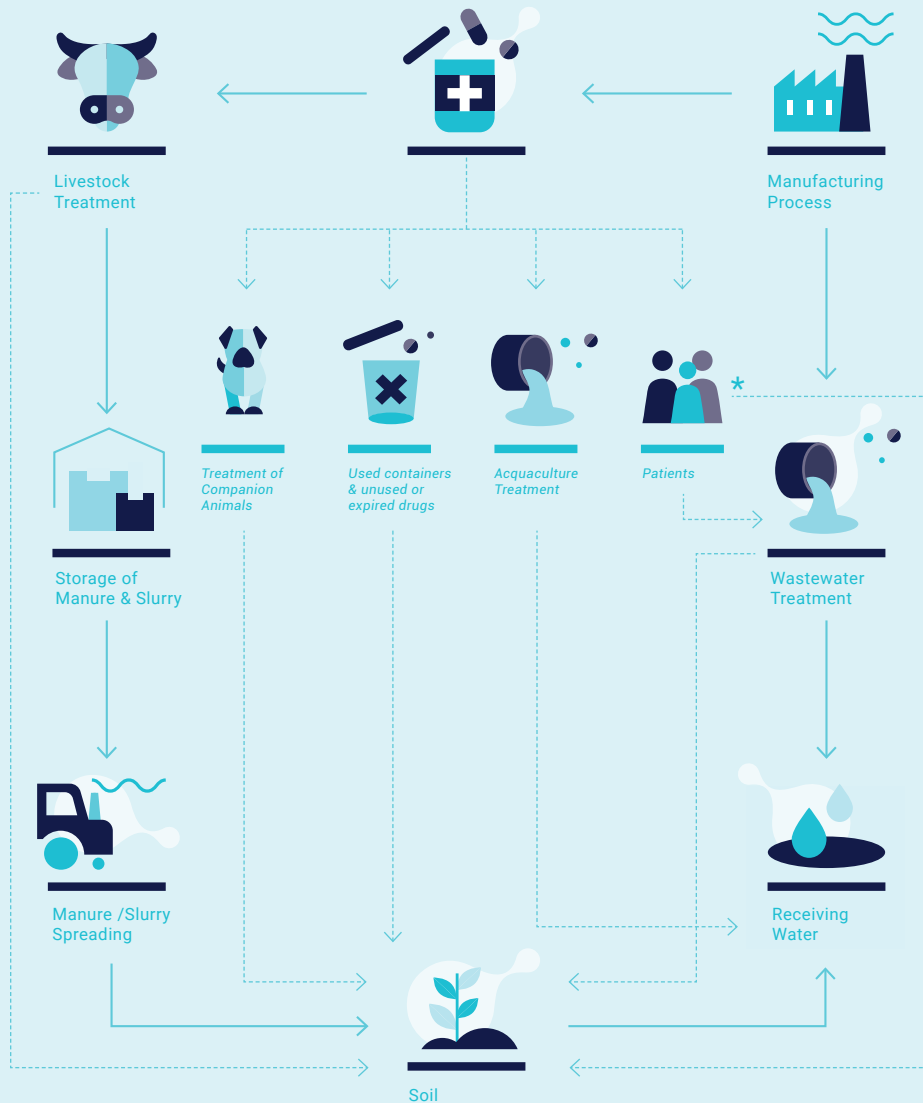


Manufacturing emissions from both the production of active pharmaceutical ingredients (APIs) and their formulation into drugs is another source of environmental emissions. In regions like Europe, only trace levels of antibiotics in the environment can be attributed to waste from production but in countries where discharges are not well controlled some studies have found very high levels of active residues in the discharge vicinity of antibiotic factories (for example, in China and India). [6-7]

Figure 1.

Main path ways of antibiotics into the environment.

Adapted and modified from: Boxall, AB. The environmental side effects of medication. 2004. European Molecular Biology Organization Reports: 5 (12).



* Applicable only to selected LMIC

The release of antibiotics in the environment in these ways can increase the number of selection pressures that cause resistance to emerge. A vast array of other contaminants, such as biocides and heavy metals, can combine to add further pressure on bacteria to become resistant.

Once resistant bacteria are in the environment, they can persist and spread through waterways and soils.

People and animals can be exposed to them through food, water and air; although more scientific studies are needed to understand the connection between the presence of antibiotics in the environment and the development of clinically-relevant resistance in humans. [4]

Manufacturing matters

Even though manufacturing emissions is not the main source of antibiotics in the environment, most stakeholders, including the pharmaceutical industry, agree on the need for common responsible manufacturing practices to minimize their risk.

The AMR Industry Alliance wants to help eliminate or significantly reduce antibiotic residues in manufacturing emissions, especially by improving waste management and by taking stronger action to prevent accidental spills and releases.

To that end, the AMR Industry Alliance has made specific commitments to reduce the environmental impact from the production of antibiotics (see box 'Alliance environmental commitments').

Alliance environmental commitments

In 2016, 13 leading members of the AMR Industry Alliance signed an AMR Industry Roadmap committing them to, among other things, reduce the environmental impact of antibiotics production. [8] In particular, they promised to:

- Review their own manufacturing and supply chains to assess good practice in controlling releases of antibiotics into the environment.
- Establish a common framework for managing antibiotic discharge; and start to apply it across their own manufacturing and supply chain by 2018.
- Work with stakeholders to develop a practical mechanism to transparently demonstrate that their supply chains meet the standards in the framework.
- Work with independent technical experts to establish science-driven, risk-based targets for discharge concentrations for antibiotics and good practice methods to reduce environmental impact of manufacturing discharges by 2020.

Measures to meet each of these commitments are complete or actively ongoing.

- What impact does environmental exposure to antibiotic resistance have on human and animal health?
- How feasible and effective are available technological, socio-behavioral and economic interventions to mitigate environmental antibiotic resistance?

More scientific studies are needed to better understand transmission pathways that may enable clinically relevant antimicrobial resistance to develop from antibiotics in the environment.

INCONSISTENT OVERSIGHT

The regulatory framework for waste and wastewater from antibiotic manufacturing varies widely from country to country. In general, active pharmaceutical ingredients are not specifically regulated in environmental laws. Inconsistency in inspection and enforcement of environmental regulations, especially in certain emerging markets, makes it particularly important that manufacturers themselves provide adequate oversight of their antibiotic suppliers to ensure responsible practices extend across global antibiotic supply chains.

DISCHARGE TARGETS

Despite the growing call to reduce emissions from antibiotic manufacturing, there is no simple mechanism that enables a global standard to be developed to control and manage antibiotic residues in manufacturing.

However, in an effort to minimize the environmental impact of manufacturing production, many pharmaceutical companies set voluntary effluent targets for pharmaceuticals as part of their own environmental programs and recently the AMR Industry Alliance published science-driven, risk-based targets for discharges for approximately 120 antibiotics (see page 30 below).

LIMITED CAPACITY

In some emerging markets, limited waste management infrastructure and a lack of environmental knowledge and experience may increase the challenge of ensuring effective control of emissions from antibiotic manufacturing sites.

What impact does environmental exposure to antibiotic resistance have on human and animal health?

Barriers to overcome

There are many theoretical and practical challenges to tackling antibiotic residues in manufacturing waste. Some of the most significant barriers are outlined below.

KNOWLEDGE GAPS

The role of the environment in the rise, spread and health risk of antibiotic resistance is an area of intense investigation, and many key questions remain unanswered. For example:

- How and to what extent do different sources of antibiotic residues and resistant bacteria contribute to resistance in the environment?
- What is the role of the environment in the evolution of resistance and how is this affected by human activities?

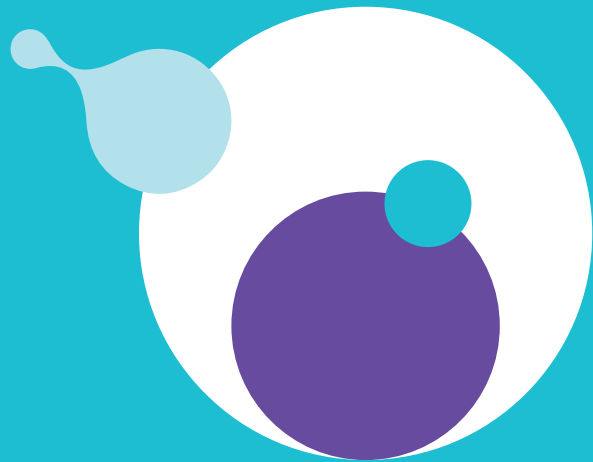


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More studies are needed to understand the transmission pathways that lead from antibiotics in the environment to clinically relevant antimicrobial resistance in homes and hospitals.

03

A common framework



As a global network of industry partners, the AMR Industry Alliance is well positioned to promote responsible antibiotic manufacturing across the world and to help develop practical tools for limiting emissions throughout the antibiotic supply chain.

In 2016, through the AMR Industry Roadmap, we promised to develop a common framework for managing antibiotic emissions.

In early 2018, we published the results of our work as a set of minimum

environmental expectations for antibiotic manufacturers (the Common Antibiotic Manufacturing Framework). [9]

The framework applies to all types of factories that make antibiotics, including those that produce antibiotic active pharmaceutical ingredients (APIs) and those that formulate those APIs into medicines. It is made up of five components: regulatory compliance; environment, health and safety (EHS) management systems; training; waste and emissions; and site audits (see Figure 2).

For each component, the framework lays out the best practices that antibiotic manufacturers should follow to minimize the environmental risk arising from their antibiotic supply business.

It not only applies to the antibiotic manufacturing sites owned or managed by alliance members, but extends to all their suppliers' sites too, vastly increasing the framework's potential for improving performance.

All AMR Industry Alliance members that supply antibiotics on a commercial basis are required to report their progress in implementing the framework (see Practical Progress below).

Figure 2.

The Common Antibiotic Manufacturing Framework developed by the AMR Industry Alliance.



1. Regulatory compliance

MINIMUM EXPECTATION

Manufacturing sites must comply with all applicable laws and regulations.

The need for manufacturers to operate within local and national legal frameworks may seem beyond question, but some suppliers—particularly those in some emerging markets or countries with weak regulatory oversight—require expert help in understanding which environmental regulations apply to the production of antibiotics.

To demonstrate regulatory compliance, manufacturers must have access to current copies of all applicable laws and regulations and be able to show that they are meeting the operational and reporting requirements of each.

Manufacturing facilities should keep copies of any required reports made to authorities, as well as all manufacturing or environmental permits and licenses needed for producing antibiotics and managing waste and emissions. All authorizations should be kept up to date and periodically self-audited for compliance.

For external suppliers of antibiotics, regulatory compliance also includes adhering to any additional environment, health and safety requirements that are in the purchasing company's standards and codes of conduct for suppliers. This may include, for example, requirements to report specific types of accidents or incidents or to share regulatory agency findings (including penalties).

In all cases, manufacturers are encouraged to take social and environmental responsibility for their production practices and go beyond meeting basic regulatory requirements to establish environmental protection goals that can evaluate and reduce potential environmental risks.

2. Environment, health and safety management systems

MINIMUM EXPECTATION

Manufacturing sites must have a robust environment, health and safety (EHS) management system in place; and periodically evaluate it for continued effectiveness.

This component of the framework acknowledges that many drug companies go beyond regulatory compliance to keep people safe, protect local environments and secure a sustainable supply of medicines.

The AMR Industry Alliance framework does not make specific requirements of EHS programs. Rather, it points to PSCI principles as a reference point for the types of policies and practices that should be in place throughout the supply chain (see 'PSCI Principles').

Many drug companies go beyond regulatory compliance to keep people safe, protect local environments and secure a sustainable supply of medicines.

The Pharmaceutical Supply Chain Initiative (PSCI) is a group of more than 40 pharmaceutical and healthcare companies that work together to promote responsible supply chain management and better business conditions across the industry.

The initiative has developed the Pharmaceutical Industry Principles for Responsible Supply Chain Management to articulate what the industry expects of its supply chain. The PSCI principles address five areas of responsible business: ethics, labor, health and safety, environment and management systems.

The principles on health and safety and environment are particularly relevant to the AMR Industry Alliance manufacturing framework; and it is these principles that alliance members and their suppliers are expected to follow.



ENVIRONMENT

PSCI principles on environment aim to ensure that suppliers operate in an environmentally responsible and efficient way. They cover:

- 01 Environmental authorizations:** complying with all applicable environmental regulations.
- 02 Waste and emissions:** establishing systems to ensure the safe handling, movement, storage, recycling, reuse and management of waste and emissions, including controlling and treating any waste or emissions with the potential to adversely impact human or environmental health.
- 03 Spills and releases:** installing systems to prevent and mitigate accidental spills and releases to the environment.



HEALTH AND SAFETY

PSCI principles on health and safety aim to ensure that suppliers provide a safe and working environment. They cover:

- 01 Worker protection:** protecting workers from over-exposure to chemical, biological and physical hazards; and from physically demanding tasks.
- 02 Process safety:** establishing programs to prevent or mitigate catastrophic releases of chemicals.
- 03 Emergency preparedness and response:** identifying and assessing emergency situations and minimizing risks and impacts through emergency plans and response procedures.
- 04 Hazard information:** using safety information about hazardous materials to educate, train and protect workers from hazards.

Find out more about the PSCI principles at: <https://pscinitiative.org/principles>

Continual improvement

In all cases, manufacturers are expected to pursue continual improvement through what is commonly known as the Plan-Do-Check-Act cycle (see Figure 3). This cycle is a standard component of EHS management and will typically already form part of manufacturers' EHS programs.

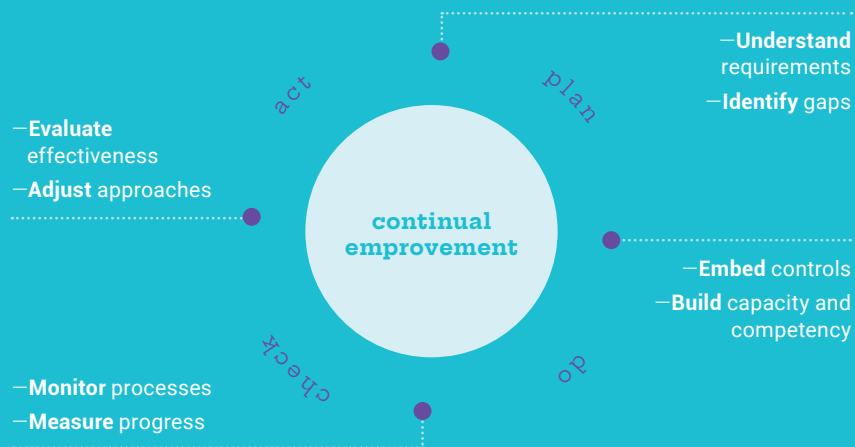
The AMR Industry Alliance recognizes that antibiotic suppliers have a range of environmental management capabilities and that supplier performance can vary.

In part, the common antibiotic manufacturing framework has been created to enable suppliers at all levels to understand the best practice expectations of them and to develop and deliver action plans to fulfil these.

In some cases, companies will need to invest in people and equipment to make the necessary improvements, which will take time. Alliance members are expected to closely monitor their suppliers' progress in implementing action plans to ensure improvement is made in a timely fashion, taking into account the need for continuity in supply of critically important antibiotics.

Figure 3.

The Plan-Do-Check-Act cycle of continual improvement.



3. Training

MINIMUM EXPECTATION

Manufacturing sites are expected to provide appropriate training, in line with industry best practice.

The AMR Industry Alliance framework does not include specific requirements for training, but again points to PSCI principles for guidance on what is meant by 'appropriate'.

In brief, the PSCI principles call for a training program that arms managers and workers with the skills and knowledge they need to perform their work safely and appropriately. Such a program should address all relevant health and safety risks identified in safety and environmental risk assessments. PSCI have five free webinars on the topic of pharmaceuticals in the environment, including one on AMR, that are a valuable training resource for manufacturers and their suppliers (see <https://pscinitiative.org/resources>).

The effectiveness of specific training should be evaluated through employee competency assessments. And the program as a whole should be regularly reviewed and updated to incorporate trainee feedback and to continually improve its design and delivery.

In the context of responsible manufacturing, effective training programs typically include specific elements to cover:

– **WASTE MANAGEMENT (SOLID AND LIQUID).** This includes training to make workers and others aware of the potential environmental risks of antibiotics in the environment and to ensure they appreciate their roles and responsibilities in controlling wastes and emissions to avoid these. More specific training may include use of waste management controls, and operating procedures. In all cases, training should be given to anyone responsible for assessing waste

management risks and for designing or operating waste management systems.

- **EQUIPMENT.** This includes ensuring that workers know how to access and use any relevant personal protective equipment or job-specific machinery.
- **HAZARDOUS MATERIALS.** This includes making workers aware of the risks associated with each hazardous material they may come across in their job; and training them on how to correctly use, classify, handle, store and dispose of these. Training on hazardous materials should include instructions on what to do if there is an incident involving specific materials.

4. Waste and emissions

MINIMUM EXPECTATION

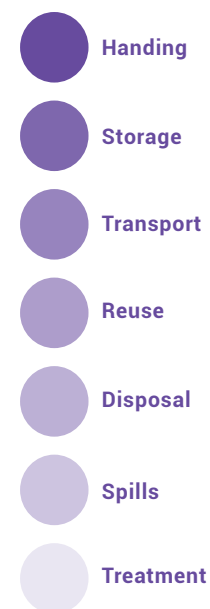
Manufacturing sites are expected to exercise appropriate duty of care for all discharges and waste streams containing antibiotics.

This is the main component of the AMR Industry Alliance framework. It sets out the requirements of alliance members and their suppliers; and it represents the area where better performance has the biggest potential to minimize the concentration of antibiotics in waste streams.

The main areas of focus here are water discharges and solid waste. The expectations set out in the framework are intended to cover typical aspects of waste management (see Figure 4); and are aligned with the PSCI principles on environment (see 'PSCI Principles' in Section 2 above).

Figure 4.

Typical elements of waste management.



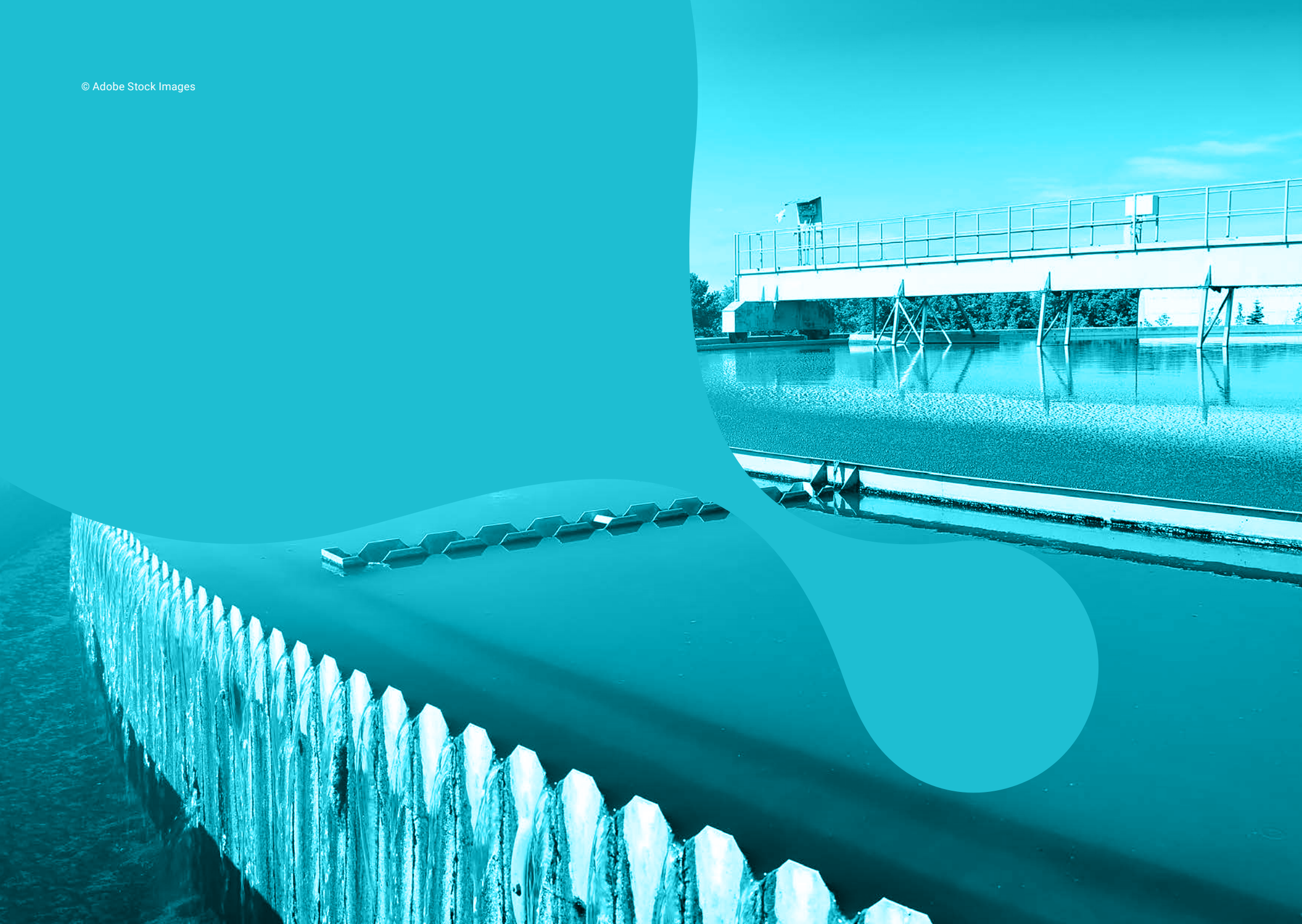
4.1 Water discharges

MINIMUM EXPECTATION

Manufacturing sites are expected to have strong systems for managing water discharges.

In particular, these must be able to effectively:

- **manage, control and treat** any wastewater or wastewater sludge with the potential to adversely impact human or environmental health before it is released to the environment; and
- **prevent and mitigate** any accidental spills or releases to the environment.



The AMR Industry Alliance framework sets out specific expectations for managing water discharges from antibiotic manufacturing sites, as outlined below.

01

Valid permits

Each manufacturing site must operate in accordance with local laws, which may require getting a license or equivalent for discharging wastewater into relevant local systems (be they groundwater, rivers or public waterways and sewers). The site must maintain systems and processes to show that it complies with every condition or requirement in the operating permit.

02

Assessment of antibiotics in waste streams

Before starting up, each manufacturing site must identify routes by which antibiotics could potentially be released to the environment; and establish and maintain environmental controls to prevent the concentration of antibiotics in wastewater exceeding scientifically derived targets (see 'Science-driven risk-based targets' on page X below).

03

Characterization of wastewater

Process wastewater with potential to contain antibiotic residues must be characterized. This includes collecting information on a number of parameters—for example, wastewater composition, toxicity, flow rates, pathways, and destinations—to evaluate control options and inform treatment and responsible disposal practices.

04

Treatment options

Each manufacturing site must provide effective wastewater treatment to remove antibiotic residues. This may include any range of physical, biological or chemical treatments aligned with the outcomes of the assessment, including for example:

- **pH or thermal treatment:** to deactivate or destroy certain classes of antibiotic.

05

Working equipment

- **Steam stripping, evaporation or reverse osmosis:** to remove specific antibiotic compounds.
- **Chemical or electrocatalytic oxidation:** to degrade antibiotics into less harmful substances.
- **Aerobic and anaerobic treatments:** to break down and remove organic substances.

All water and wastewater monitoring devices and treatment systems used at each manufacturing site must be in good working order and appropriately maintained, in accordance with the manufacturer's recommendations.

06

Wastewater sampling and reporting

If manufacturing facilities choose to do wastewater sampling to support their risk assessment, they must use defined methods for collecting, storing, transporting and analyzing samples. These must be in line with the site environmental authorization and results reported, as per local regulatory requirements.

07

Drinking water testing

Any drinking water systems (on or off site) that could be impacted by contamination from antibiotic manufacturing must be tested for compounds of concern, including for example, any antibiotics produced or used.

08

Spill prevention

All process areas on manufacturing sites—including, for example, tanks, container storage areas, and process sewer systems—must be designed, built and operated to prevent spills or releases to the environment.

09

Pollution prevention

Each manufacturing site must have systems in place to prevent the contamination of soil, surface water and groundwater with antibiotics (see also expectations on spill prevention above and biomass and sludge management under solid waste management below).

Science-driven risk-based targets

Uncontrolled manufacturing water discharges have the potential to release antibiotic residues into the environment. Effluents with low levels of antibiotics may be harmful if the concentration is too low to kill exposed bacteria but high enough to exert selection pressure for resistance. The critical question is where does the threshold lie?

At what concentration do antibiotics have no selective effect on environmental bacteria?

Many stakeholders have emphasized the need to reach global agreement on a discharge target for manufacturing wastewater that is sufficiently low to protect against the risk of increasing AMR. To that end, the AMR Industry Alliance convened an expert committee of environmental toxicologists, risk assessors, microbiologists, and engineers to review the state of the science and establish discharge targets for antibiotic manufacturing, based on Predicted No-Effect Concentrations (PNECs), for use in environmental risk assessments of antibiotics (see 'Twin measures').

Their results were published in a peer-reviewed article in 2019 and have since been adopted by the AMR Industry Alliance. [10-11] All our manufacturing members and suppliers are expected to use their best efforts to meet the new science-driven risk-based PNECs, which may take some time to achieve, especially if there is a need for process changes or capital investments. AMR Industry Alliance members are committed to report their progress to the alliance every two years (see Practical Progress on page 36).

Twin measures

The AMR Industry Alliance science-driven risk-based targets for discharges are developed from predicted non-effect concentrations (PNECs), and include two elements:



Environmental predicted no-effect concentrations (PNEC-ENV) focus on protecting local environments from toxic contamination. They are calculated using traditional ecotoxicological endpoints, for example growth inhibition of cyanobacteria.



Resistance predicted no-effect concentrations (PNEC-MIC) aim to protect against the promotion of antibiotic resistance by lowering selective pressures. They are derived from data on minimum inhibitory concentration (MIC), which is a common method for determining how susceptible a bacterium is to antibiotics. The PNEC-MIC calculations combine clinical MIC data with relevant safety factors to estimate the lowest concentration at which resistance might develop.

Manufacturing sites can combine these PNECs with local parameters to establish a site-specific safe discharge concentration target that can be used to minimize the potential for contributing to AMR in the environment. If discharge concentrations are found to exceed this target, management of the manufacturing site should reassess its manufacturing and associated waste management processes to identify further controls that can reduce the concentration of antibiotic in wastewater to below the target.

In line with best practices set out in the 2018 European Union Water Framework Directive, the PNEC-based targets are compared with antibiotic concentrations predicted or measured in the 'mixing zone' of the receiving aquatic environment, rather than at the end of a discharge pipe or in a wastewater treatment plant.

Opportunities and obstacles

The risk-based PNEC targets cover around 120 APIs used in antibiotic manufacturing. They have been calculated using the best available science, based on a combination of industry data and peer-reviewed literature. The first of their kind, these targets represent huge progress in building a quantitative foundation for good practice methods to reduce the environmental risk of antibiotic manufacturing discharges.

Beyond manufacturing, the new PNEC targets may also prove useful in other settings. For example, they can help inform risk assessments of municipal waste streams, as long as there is due consideration of other contaminants beyond antibiotic residues (such as metals or biocides) that can add selection pressure for resistance.

In all cases, the PNEC targets are expected to evolve as the science of antimicrobial resistance and of the environmental contribution to clinically relevant resistance continues to advance.

4.2 Solid waste management

MINIMUM EXPECTATION

Manufacturing sites are expected to have strong systems for managing solid waste. In particular, these must be able to:

- ensure the **safe handling, movement, storage, recycling, reuse** and disposal of waste;
- provide adequate **control and treatment** of any waste with the potential to adversely impact human or environmental health; and
- effectively **prevent and mitigate** any accidental spills or releases to the environment.

The AMR Industry Alliance framework sets out several expectations for managing solid waste from antibiotic manufacturing sites, as outlined below.



LABELING AND DISPOSAL

All solid wastes must be classified, labeled and disposed of according to their hazard characteristics and in line with applicable laws and regulations. In particular:

- All waste containers must be labeled to show the type and hazard characteristics of their contents, for example whether they are flammable or biological. And all containers must be closed once waste is put inside them.
- All disposal methods must be based on the characteristics of the waste and must be fully recorded. This includes, for example, keeping records of waste classifications (including analytical results) along with letters from waste contractors and certificates of destruction.

In addition, all waste disposal contractors used by manufacturers must have a license, permit or other appropriate authorization to manage waste; this must be issued by the relevant regulatory authority and must cover the specific waste stream at hand.



STORAGE

Across every manufacturing site, waste must be stored in a way that prevents contaminated discharges and unsafe conditions. In an effective storage system:

- Storage containers are in good condition and are compatible with the materials being stored in them (by

being, for example, free from corrosion, dents and bulges). They are kept closed at all times, except when being filled or emptied.

- Material is stored in such a way to avoid unwanted reactions, decomposition or self-ignition. In all cases, it is stored in quantities within the relevant spill containment capacity and is kept sheltered from the weather.
- Solid wastes are stored in such a way to prevent any discharge from rain or storm water run-off.
- Incompatible wastes (for example, acids and bases) and their spill containment measures are properly segregated.
- The integrity of spill containment measures is regularly inspected, documented and maintained.



FIRE RISKS

All waste storage areas on manufacturing sites must be segregated, with access limited to authorized personnel.

In addition, the fire risks associated with each waste storage area must be assessed; and suitable fire management and prevention measures must be in place. This includes, for example: using smoke detectors and separation walls; ensuring that fire extinguishers are easily accessible and in working order; and, where appropriate, building firewater retention facilities to hold any spent firewater until it can be disposed of safely.



LANDFILLS

Any landfills or permanent waste disposal areas on manufacturing sites must be specifically authorized by regulatory authorities. Each one must also be subject to regular monitoring and maintenance to ensure effective containment.



SPILL AND CONTAMINATION PREVENTION

All process areas on manufacturing sites—including, for example, waste storage areas and process systems—must be designed, built and operated to prevent spills or releases to the environment.

Each manufacturing site must also have a program to manage soil or groundwater contamination from spills. Any unpermitted or accidental release of solid waste to the environment must be reported to the proper authorities and remedial measures must be implemented to address any adverse impacts associated with the incident and to prevent it from happening again.

5. Site audits

MINIMUM EXPECTATION

Manufacturing sites are expected to allow and facilitate on-site audits of their operations to ensure they meet the expectations of the common framework.

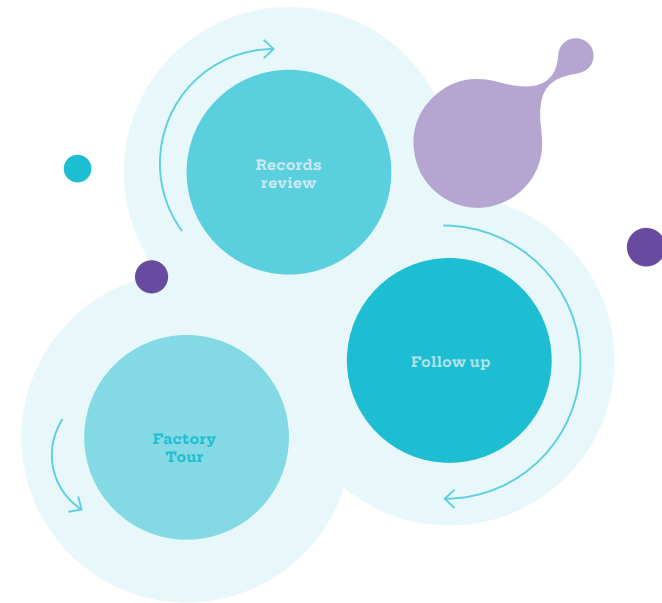
This component of the framework applies to all manufacturing sites, especially those belonging to external suppliers of AMR Industry Alliance members. The focus on suppliers is seen as the most effective way of extending the framework's reach throughout the supply chain.

In all cases, on-site audits should be done at least every five years; they should focus on environmental management, specifically water and waste management, spill prevention and response, chemical storage and handling, and employee training. It is worth noting that since the common framework was published, the PSCI has incorporated it into its auditing programme so that any company going through a PSCI shared audit will be assessed against the declaration of the AMR Industry Alliance framework (among other things).

Audit reports

All audit reports will remain confidential between the company and the supplier or manufacturing site being audited. Companies that are members of PSCI can choose to share their audit reports through the PSCI data base, as long as the supplier has given their permission to do so.

Companies can also choose to publicly report aggregate audit information as part of their overall EHS program reporting.



Each audit should comprise three main activities:

01

Records review

A records review is used to ensure regulatory compliance and evaluate company policies and procedures. It includes assessing:

- regulatory requirements and permit statuses;
- maintenance plans for critical equipment and environmental controls;
- incident investigation reports, including corrective and preventative action plans;
- waste and wastewater disposal records;
- environmental risk assessments (including estimates of antibiotic discharges quantified through mass balance or measurement and how these compare with PNEC targets); and
- supplier practices for evaluating their own supply chain.

02

Factory tour

A factory tour is used to assess operating practices and conditions in and around the manufacturing site. It includes an external tour of the entire factory, including discharge locations, pollution control devices and receiving streams, with specific identification and observation of:

- systems for collecting and treating process and domestic wastewater, and for collecting and retaining storm water;
- water extraction practices, including any deep wells;
- storage tanks (above or below ground) and associated visible piping;
- waste storage facilities and practices;
- any on-site wastewater treatment plants;
- fuel storage locations;
- solvent storage and recovery facilities;
- warehouses and any other physical storage sites; and
- any firewater retention facilities.

03

Follow up

Once the reports review and factory tour are complete, every audit should be followed up with:

- A clear report that identifies any problem areas or mismatches in policy and practice.
- Supportive follow up to ensure that the audited supplier develops corrective action plans and implements them over time. This includes sharing knowledge and technical expertise as and where appropriate to help address gaps in practice.
- Strong oversight to monitor performance and ensure the appropriateness of ongoing supplier relationships.



04

Practical progress

Biennial assessment

All manufacturing members of the AMR Industry Alliance are expected to report on their progress in implementing the common framework. This is done through self-assessments (of their own sites as well as of those of their suppliers) submitted to the alliance every two years. Aggregated findings are communicated to the public through the AMR Industry Alliance Progress

Report*. Our first progress report was published in 2018, and with it, the full text of the common antibiotic manufacturing framework. [12]

The report summarized the general status of manufacturing action to reduce the potential environmental impacts of antibiotics manufacturing on AMR at that time (see 'Starting status').

* See www.amrindustryalliance.org/progress-report

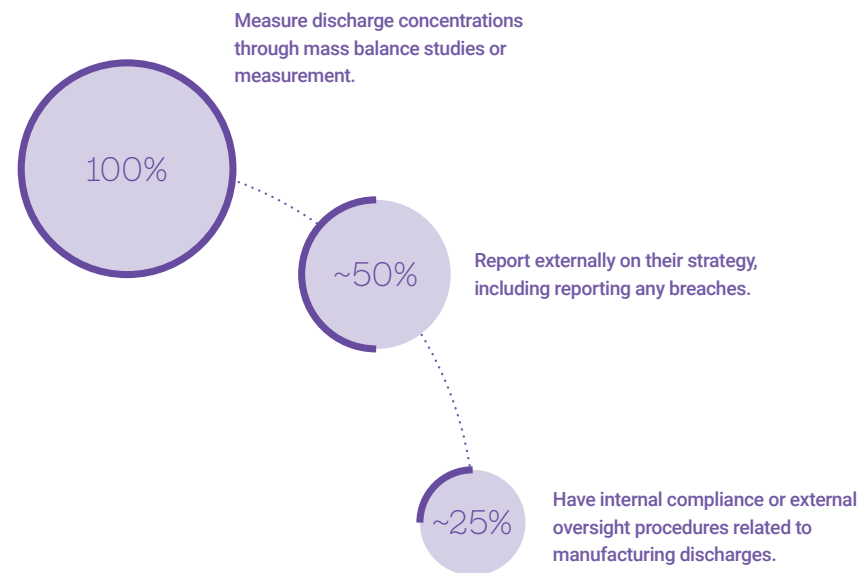
Starting status

Two thirds of responding companies that produce antibiotics have a strategy, policy or plan to address the environmental impact of their business operations, and those of their suppliers, on antibiotic resistance.

This includes, for example:

- Increasing the public transparency of findings about suppliers.
- Inserting new checks and balances into supplier contracts.
- Improving the oversight or monitoring of suppliers.

One third of responding companies that produce antibiotics have a strategy, policy or plan to address the release of antibiotics in internal manufacturing effluents. **Of these:**



Source: SustainAbility. Tracking Progress to Address AMR. 2018. AMR Industry Alliance: Geneva.

Innovative approaches

The first AMR Industry Alliance progress report used a selection of case studies to showcase the different types of approaches that were already being deployed across the antibiotic manufacturing sector at the time to address concerns about antibiotic discharges into the environment. These include, for example:

- Using enzymatic production processes, which have no need for chemical solvents and so are more environmentally sustainable as well as being more energy efficient.
- Building dedicated wastewater treatment plants at manufacturing sites to remove antibiotic residues before discharging into the environment.
- Installing zero-liquid-discharge equipment in antibiotic factories to recycle and reuse wastewater and keep antibiotic residues (and other APIs and resistance-contributing compounds) out of the environment.
- Funding research to study public environmental and clinical data on the impact of antibiotics and identify environmental protection goals that can be applied to antibiotic manufacturing sites.



05

Conclusion



Collaboration counts

How far and fast antibiotic resistance develops and spreads is governed by a diverse range of factors, both natural and man-made, that span across multiple sectors, including human and animal health, pharmaceuticals, food and agriculture, environment, education, trade and finance.

This makes antibiotic resistance one of the most complex public health challenges the world has ever faced. Meeting that challenge is beyond the ability of any single organization, government or industry. Curbing antibiotic resistance requires deliberate coordination and collaboration across different states, sectors and stakeholders. [14-15]

The AMR Industry Alliance is committed to playing its part and to supporting the global push to tackle antibiotic resistance by finding sustainable solutions to some of the most intractable problems facing this joint effort.

The common antibiotic manufacturing framework (including the PNEC targets) has been developed as one such solution. In building, and now implementing, the framework, the alliance has fulfilled two of the principal commitments made in the 2016 Industry Roadmap to combat AMR.

All members of the AMR Industry Alliance are expected to implement the framework across their supply chain; and all are committed to reporting their progress in doing so. But the framework is not only for alliance members or their suppliers. It has been designed to apply to any antibiotic manufacturing site, and we strongly encourage all antibiotic manufacturers to use it to review and reduce the environmental risk of their business operations.

We note that the framework is embedded in a rapidly evolving branch of science and as such, is likely to develop further over time, as we improve our evidence and understanding of the presence and impact of antibiotics in the environment and the risks these pose to human health.

Concerted efforts

Reducing the environmental risk of antibiotic manufacturing is just one piece of the AMR puzzle. Real progress will not be achieved without concerted efforts from all stakeholders to also address other environmental risks while simultaneously strengthening antibiotic stewardship, fostering the discovery and development of novel drugs, vaccines and diagnostics, and improving access to high quality antibiotics for those who need them most (see 'Priorities for action').

The AMR Industry Alliance is committed to contributing to all four critical areas of action; and we are already working to increase our members' engagement in each one as appropriate to their business.

We invite other companies to join us: whether you have a long history of combating AMR or have only recently joined the

fight, we will support you in your efforts and work together to advance the life-sciences industry's contribution to this global challenge.

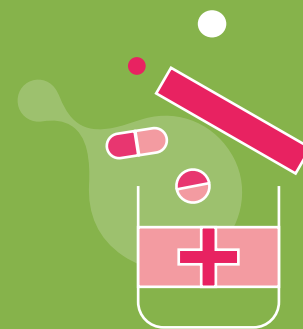
We stand ready to work in partnership with countries, healthcare providers, international agencies, donors, nongovernment organizations, academia and civil society to coordinate our efforts and find the right solutions for different nations, health systems, and products.

We welcome comments and feedback on our efforts from all stakeholders.

Contact us at info@amrindustryalliance.org.

Priorities for action

Beyond reducing concentrations of antibiotics in manufacturing discharges, concerted action is needed across four key areas:



Appropriate use

Antibiotics should only be used by patients (human or animal) who need them. Ensuring appropriate use requires a multi-pronged approach that can simultaneously lower the burden of infection (to reduce the overall need for antibiotics) while improving prescribing practices and patient behaviors (to reduce misuse of antibiotics). Some priority actions include: improving infection prevention and control; improving diagnostics (including new technologies for rapid bacterial identification); increasing education and awareness of healthcare professionals, veterinarians and the general public; expanding collection and transparency of antibiotic consumption data (in humans and animals); eliminating the use of any antibiotics for growth promotion in agriculture; and restricting the use of critical antibiotics across all sectors.



Access

An estimated six million people die each year from infections because they lack access to antibiotics. Enhancing access is about making existing and new drugs, diagnostics and vaccines more available and more affordable; if accompanied by effective stewardship, it can save lives and slow the spread of resistance. Some priority actions include: strengthening supply chains, building regulatory capacity, securing fair pricing and donations, and eliminating false and substandard drugs.



Innovation

Innovation transects all aspects of the fight against antibiotic resistance. In part it is about re-invigorating the discovery and development of new antibiotic compounds and products so that we do not run out of options for treating infections. That requires a range of actions to secure sustainable investment in R&D for new antibiotics and alternatives. In part innovation is about leveraging research (including operational research, social science and behavioral studies) to support better stewardship and access. And in part innovation is about improving our basic understanding of where and how antibiotic resistance develops and spreads, with a particular need for more 'One Health' research to understand transmission pathways.



Environment

Antibiotic manufacturing is not the only environmental risk for AMR; contamination can also occur from human and animal waste and from the use of antimicrobial pesticides for crops. Some priority actions for addressing these include: setting evidence-based standards for hospital waste treatment; improving hygiene and sanitation (including more effective waste disposal and treatment); improving biosecurity; and developing alternative disease prevention and control strategies for livestock and crops.

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AMR Industry Alliance
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The AMR Industry Alliance brings together biotech, diagnostics, generics and research-based pharmaceutical companies, to drive and measure industry progress to curb antimicrobial resistance.

The rapid rise in antibiotic resistance threatens to reverse a century of progress made by modern medicine. Experts warn that without immediate and worldwide action to curb this global threat, we may be forced into a future in which routine operations, simple wounds and common infections could once again prove fatal.

Avoiding this post-antibiotic era requires all countries, companies and communities to join forces and change the ways we make, regulate and use antibiotics. One thing that the life sciences industry can do to help is to protect local environments by effectively minimizing the presence of antibiotic residues in pharmaceutical production waste streams. To that end, the AMR Industry Alliance has developed a common framework for responsible antibiotic manufacturing, which lays out the best practices that factories producing antibiotics should follow to minimize the environmental risk of their business. For the first time ever, antibiotic manufacturers also have a set of science-based target concentrations for antibiotics in receiving waters they can use to shape their environmental and waste management strategies and ensure the continued health and safety of people and the planet.

More than 100 companies across the life sciences industry are members of the AMR Industry Alliance and are committed to taking actions appropriate to the nature of their business to address AMR risk. This includes approximately 20 producers of antibiotics that are working to implement the manufacturing framework, both in their own operations and in those of their suppliers.

AMR Industry Alliance
Chemin des Mines 9
PO Box 195
1211 Geneva 20
Switzerland
www.amrindustryalliance.org

