

Antibiotic manufacturing standard

Minimizing risk of developing antibiotic resistance and aquatic ecotoxicity in the environment resulting from the manufacturing of human antibiotics

JUNE 2022

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Foreword

Publishing information

The AMR Industry Alliance (AMRIA) engaged BSI Standards Limited to provide expert services in relation to the development of this antibiotic manufacturing standard. This included engaging the technical author Jessica Vestel of MSD to produce an initial draft, editing the draft in accordance with BSI Rules for the structure and drafting of UK standards and providing an updated draft to The AMR Industry Alliance for further development.

This private standard is not to be regarded as a BSI publication, such as a British Standard, a BSI PAS or a BSI Flex. Work by BSI was completed in May 2022.

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0.0 Introduction

0.1 Background

With the significant rise in death toll across the globe, antibiotic resistance (ABR) has become a major global health concern that threatens to undermine the basis of modern medicine by rendering the antibiotics used to treat and prevent infectious disease ineffective (e.g. during invasive surgery) [1].

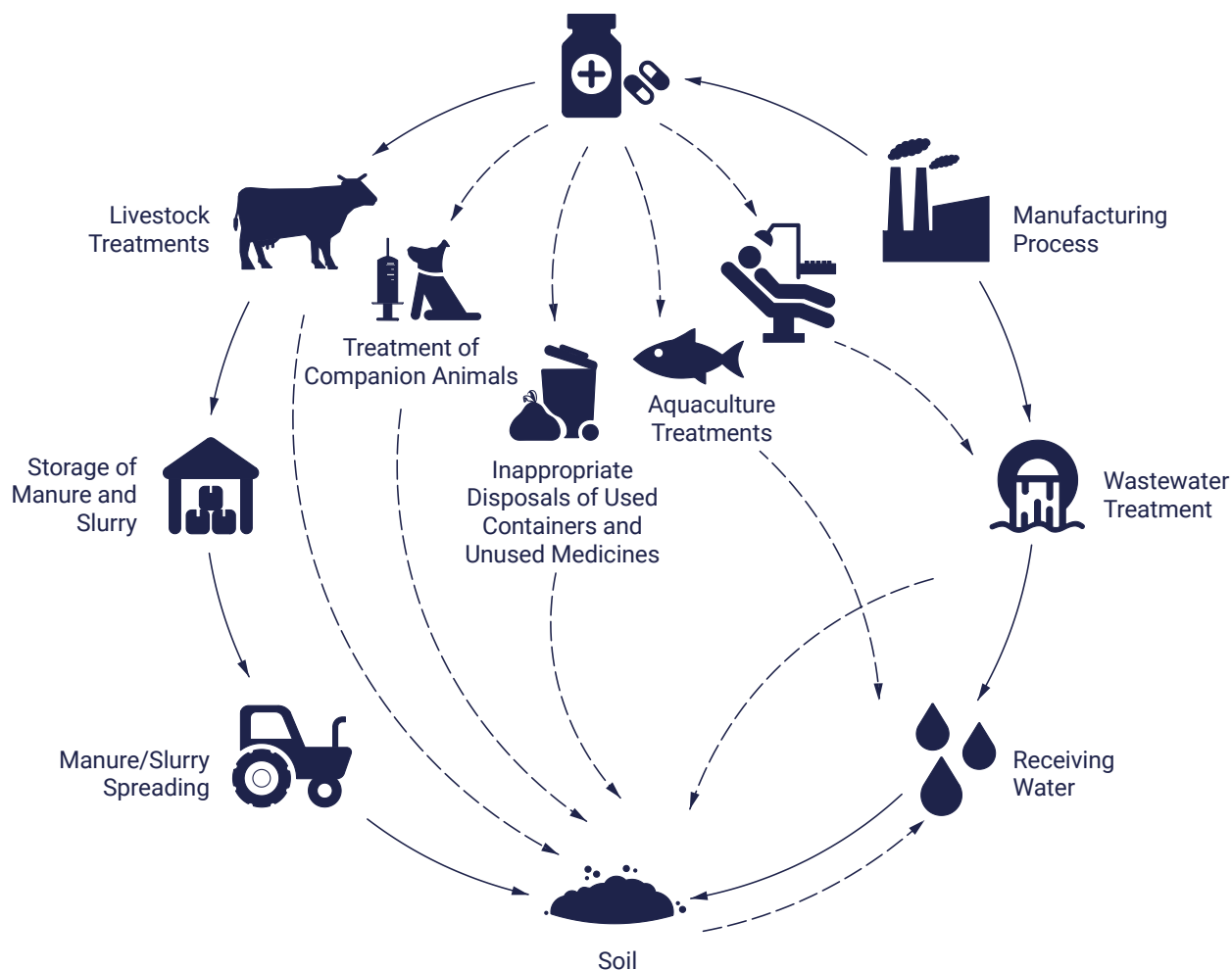
There are several causes of ABR, including over and misuse of antibiotics in human and animal health in the agriculture and aquaculture sectors. Human health is inextricably linked to environmental health and as such there are concerns that the presence of antibiotics in the environment may also contribute to antibiotic resistance in humans through the development and subsequent spread of resistance in environmental bacteria.

0.2 Pharmaceuticals in the environment

While the major source of pharmaceuticals in the environment (PiE) is believed to result from patient use of medicine and subsequent excretion, other sources can include industrial emissions during the manufacture of pharmaceuticals. See Figure 1.

In general, emissions of active pharmaceutical ingredients (APIs) are not regulated globally. Some companies go beyond compliance with the basic regulatory requirements for chemical manufacturers (e.g. control of pH, biological oxygen demand, chemical oxygen demand) by establishing environmental protection goals to evaluate and reduce potential environmental risks from production of their products. Most programs, however, focus on potential toxicity to aquatic species, inefficiencies in wastewater treatment plants or potential toxicity to humans from drinking water consumption.

Inadequate management of pharmaceutical manufacturing discharges can lead to negative local impacts on the environment. In the case of antibiotics, the potential exists that elevated presence of antibiotics in the environment could increase the rate of ABR selection, although the relationship and significance of environmental reservoirs of resistance and adverse human health impacts is still under investigation. This highlights the importance of effective control of API emissions from manufacturing, both in production of the API itself and its formulation into drug products for patient use, and science-based receiving water targets for antibiotics discharged from manufacturing operations.



SOURCE: Boxall, A. The environmental side effects of medication. 2004. European Molecular Biology Organization Reports: 5 [2].

Figure 1

Sources of antimicrobials in the environment

Figure 1 illustrates how pharmaceuticals (including antibiotics) can enter the environment from numerous sources.

0.3

AMR Industry Alliance (AMRIA) work

The AMRIA is committed to minimizing the risk of antibiotic resistance developing as a result of antibiotic manufacturing waste streams that might contain antibiotic residues entering the environment. To this end, the AMRIA created and published the common antibiotic manufacturing framework in 2018 [3] which describes a risk-based approach to assessing and controlling antibiotic manufacturing waste streams.

Having shared the framework broadly and having shared AMRIA members' progress towards implementing the requirements of the framework, the AMRIA decided to codify the framework requirements in this antibiotic manufacturing standard. In creating this standard, the opportunity has been taken to update key requirements based on extensive AMRIA member implementation experience, incorporation of antibiotic predicted no-effect concentrations (PNECs), and inclusion of feedback from interested stakeholders.

NOTE

The AMRIA also intend to develop an accompanying certification scheme. Such a scheme would enable antibiotic manufacturers to seek independent certification that the process which creates each antibiotic product follows the requirements of the standard.

1.0 Scope

This antibiotic manufacturing standard specifies requirements to reduce the development of ABR and the risk of aquatic (surface water) ecotoxicity in the environment resulting from antibiotic manufacturing operations.

This antibiotic manufacturing standard covers the process of commercial manufacture of antibiotics intended for human use API; and antibiotics as part of drug product formulations containing the drug substance.

A site might manufacture multiple antibiotic APIs and/or final dosage forms containing antibiotics, and each process is to follow the requirements of the antibiotic manufacturing standard.

This antibiotic manufacturing standard also covers:

- a) the management of antibiotic process wastewaters discharged during manufacturing to meet predicted no-effect concentration (PNECs);
- b) methods to minimize the amount and concentration of antibiotics lost to wastewater;
- c) handling, treatment and disposal of other antibiotic waste to minimize or eliminate release of antibiotics into the environment; and
- d) processes and systems to demonstrate conformity to this antibiotic manufacturing standard.

This antibiotic manufacturing standard excludes non-antibiotic APIs or other hazardous chemicals, products prior to commercialization (e.g. development or clinical trials), intermediate chemicals used in antibiotic manufacturing processes and patient use of antibiotics.

This antibiotic manufacturing standard does not cover non-ABR related and non-ecotoxicity related environmental impacts that might arise from antibiotic operations, including but not limited to:

- 1) energy use;
- 2) greenhouse gas emissions;
- 3) volatile organic compound (VOC) emissions;
- 4) air emissions, such as CO₂ or nitrous oxides from boilers;
- 5) non-antibiotic parameters typically included in aqueous permits such as biochemical oxygen demand (BOD), chemical oxygen demand (COD), pH; and
- 6) solid waste not containing antibiotic residues.

This antibiotic manufacturing standard is intended for use by antibiotic manufacturers. It may also be of interest to other pharmaceutical industry manufacturers and stakeholders with an interest in antibiotic manufactures and their antibiotic suppliers, such as non-governmental organizations, academia, investors, buyers of antibiotics, and local and national governments.

2.0 Normative references

There are no normative references in this standard.¹

3.0 Terms, definitions and abbreviations

For the purposes of this standard, the following terms and definitions apply.

3.1 Terms and definitions

3.1.1 active pharmaceutical ingredient

biologically active ingredient in a pharmaceutical drug

3.1.2 antibiotic

medicine used to prevent and treat bacterial infections

3.1.3 antibiotic resistance

acquired ability of a bacterial strain to withstand antibiotic exposure better than a wild-type bacterium of the same species

3.1.4 antibiotic waste

waste (solid or liquid) that is suspected to be contaminated with antibiotic API, regardless of concentration

3.1.5 antimicrobial resistance

acquired ability of a strain of bacteria, viruses, fungi or parasite to better withstand treatment with antimicrobials than the corresponding wildtype organisms

3.1.6 effluent

treated or untreated wastewater that flows out of a treatment plant, sewer, or industrial outfall

1. Documents that are referred to solely in an informative manner are listed in the Bibliography.

3.1.7 **manufacturing**

processes which create medicines

NOTE *Including the creation of the API and drug product formulation.*

3.1.8 **minimum inhibition concentration**

lowest concentration of an antibiotic that inhibits 100% of the visible growth of a given strain of bacteria after 24-hour incubation

3.1.9 **pharmaceuticals in the environment**

presence of pharmaceuticals in environmental compartments

NOTE *Such as in surface water, ground water and soils.*

3.1.10 **point of generation**

initial removal of materials from the manufacturing process with the intent of disposal

3.1.11 **predicted environmental concentration**

calculated concentration of a chemical in the environment, typically using modelling

3.1.12 **predicted no-effect concentration**

concentration of a chemical, below which adverse effects in the environment are not expected to occur

3.1.13 **receiving water**

river, ocean, stream, or other watercourse into which wastewater or treated effluent is discharged

3.1.14 **risk quotient**

measure of risk that compares the predicted environmental concentration to the predicted no-effect concentration ($RQ = PEC/PNEC$)

3.1.15 **secure landfill**

waste storage facility designed and operated to prevent release into the environment

NOTE *For example through impermeable liners and leachate collection systems.*

3.1.16**solid waste**

solid material containing antibiotic residue and generated from manufacturing including, but not limited to fermentation biomass, pollution control device solids, wastewater treatment plant sludge, contaminated packaging

3.1.17**wastewater treatment plant**

facility that aims to remove contaminants through a combination of processes in order to produce effluent suitable for intended discharge

NOTE *Examples of processes used include physical, chemical and biological.*

3.1.18**zero liquid discharge**

wastewater management system for the maximum recovery of water from wastewater

NOTE *The water is beneficially reused (e.g. in boilers and cooling towers) after treatment. In the case of land application of treated water (e.g. landscape use), proper risk assessment and controls are to be done. The salts and other solids removed from the wastewater are properly disposed in a manner which does not allow release to water (e.g. incineration, contained landfill).*

3.2**Abbreviations**

For the purposes of this standard, the following abbreviations apply.

ABR	antibacterial resistance
AMR	antimicrobial resistance
API	active pharmaceutical ingredient
MIC	minimum inhibition concentration
PEC	predicted environmental concentration
PiE	pharmaceuticals in the environment
PNEC	predicted no-effect concentration
POG	point of generation
RQ	risk quotient
WWTP	wastewater treatment plant
ZLD	zero liquid discharge

4.0 Wastewater management program

COMMENTARY ON CLAUSE 4

The level of detail and complexity of the environmental management system varies depending on compliance obligations and the nature of activities, including environmental aspects and associated environmental impacts. Compliance obligations can arise from mandatory requirements, such as applicable laws and regulations, or voluntary commitments, such as organizational and industry standards, contractual relationships, codes of practice and agreements with community groups or non-governmental organizations.

4.1 General principle

Antibiotic concentration in manufacturing wastewater discharge shall not increase the risk of antibiotic resistance (AMR) developing in bacteria in the environment.

The user shall assess wastewater discharges containing antibiotic to determine the concentration of antibiotic(s). This predicted environmental concentration (PEC) shall be less than the concentration believed to result in increased selection pressure on bacteria in the environment, known as the predicted no-effect concentration (PNEC). Where necessary the user shall apply controls or treatment to achieve the PNEC, where:

$$\text{PEC} / \text{PNEC} = \text{Risk Quotient (RQ)}$$
$$\text{RQ} < 1$$

Risk assessment measures shall be documented (see 4.4). Measures to control emissions shall be in accordance with 4.4. and 4.5.

4.2 Demonstrating authorization/license/permit compliance

4.2.1 General

As required by local regulation, the user shall hold an authorization/license/permit to discharge treated wastewater directly to the environment or to a downstream off-site wastewater treatment plant (WWTP) owned and operated by a third party (i.e. a privately-owned WWTP or publicly-owned treatment works (POTW) or other sewerage treatment facility).

4.2.2 Authorization/license/permit conditions

The user shall have each condition identified and have a system in place that monitors, assesses and demonstrates compliance.

4.2.3 Wastewater treatment and monitoring

Effective wastewater treatment shall be provided. Wastewater monitoring devices and treatment systems shall be in good operating condition and be appropriately maintained.

4.2.4 Record keeping

Monitoring data shall be maintained and readily available, including information required by permit(s) and the operations used to demonstrate adequate control of wastewater discharges (e.g. WWTP operations). Equipment maintenance records shall be maintained.

4.2.5 Reporting

Routine and deviation reporting shall occur in a timely manner and be in accordance with permit conditions.

4.2.6 Permit deviations

Reportable deviations shall be investigated, with corrective and preventative action (CAPA) plans developed to minimize deviation re-occurrence.

4.3 Characterizing wastewater discharges

Wastewater sources from operations shall be characterized and controlled to risk quotient ($RQ < 1$). Supporting documents, such as water balances, process flow diagrams and criteria for allowable discharge to wastewater shall be maintained and made readily available.

4.4 Quantifying and assessing antibiotic discharges

COMMENTARY ON 4.4

When the PEC is less than the PNEC ($RQ < 1$), the risk to the environment is considered low, indicating that wastewater discharges are effectively being managed. When the PEC is greater than the PNEC ($RQ > 1$), there is the potential for environmental impact and wastewater discharge control practices are to be taken for adequate risk mitigation, i.e. $RQ < 1$. Case studies demonstrating how this works, with examples where $RQ < 1$ which meets the standard and $RQ > 1$ which does not meet the standard, are illustrated in Annex C.

4.4.1 General

Antibiotic residue in wastewater shall be quantified and assessed against environmental protection criteria to measure risk. Risk shall be measured by the risk quotient (RQ), which is a comparison of the predicted environmental concentration (PEC) of an API in the environment resulting from a site's wastewater discharge to the predicted no-effect concentration (PNEC).

4.4.2

Predicted environmental concentration (PEC)

COMMENTARY ON 4.4.2

The PEC is the concentration of antibiotic in the receiving water (i.e. river, lake, ocean) resulting from a manufacturing discharge. It is determined by quantifying API losses to wastewater through mass balance and/or analytical testing and applying appropriate API treatability and dilution factors. These factors are often site-specific and depend on API characteristics, wastewater treatment plant technologies and the ultimate discharge point into the environment.

The user shall make available any supporting documentation, including:

- a) mass balances: the total mass of antibiotic(s) lost during all manufacturing campaigns is established; losses allocated to wastewater are determined through batch record review;

NOTE 1 *Guidance on estimating actual API losses from the manufacturing process (calculation of a PEC) is available from the Pharmaceutical Supply Chain Initiative (PSCI) [4].*

- b) analytical testing: analytical testing is not required, however if testing waste streams for antibiotic residue, testing is used to supplement the mass balance calculations or it is used to determine the antibiotic concentration at the site end-of-pipe (EOP);
- c) the analytical method shall have sufficient sensitivity to be able to detect an antibiotic concentration at a limit of quantification to allow for comparison to the PNEC, inclusive of downstream dilution factors.

NOTE 2 *Sampling guidance is available from the Pharmaceutical Supply Chain Initiative (PSCI) [4] and Caldwell, et al., 2016 [5].*

- d) API treatability: the fate of API in wastewater treatment shall be established through site-specific testing and/or through relevant literature values (OECD testing, comparative treatment operations or through modelling). When no site-specific testing or relevant literature values are available, the API treatability default shall be 0%; and

NOTE 3 *Assessment models are available, which can be used to refine the PEC based on the inherent properties of the antibiotic (e.g. fate in a wastewater treatment plant using assessment tools such as SimpleTreat)*

- e) receiving water dilution factors: where available, local dilution factors shall be derived from known flow rates or through modelling. Low flow conditions (e.g. 10th percentile, 7Q10) or applicable mixing zone factors (e.g. chronic mixing zone for an ocean or lake discharge) shall be applied. When low flow data is unavailable, 33% of the average flow shall be applied. If local dilution is not known, standard dilution factors can be used (i.e. 10 for a river and 100 for an ocean discharge).

NOTE 4 *Environmental models are available, which can be used to calculate the dilution of the discharged effluent (e.g. CORMIX).*

NOTE 5 *Guidance for estimating dilution factors is available from the Pharmaceutical Supply Chain Initiative (PSCI) [6].*

4.4.3 Predicted no-effect concentration (PNEC)

COMMENTARY ON 4.4.3

The PNEC is the API concentration in the environment where no impact is expected. For environmental toxicity, the PNEC (known as the PNEC ENV) is derived by assessing the effective concentration where 10% effects are observed (EC10) or the no-observed effect concentrations (NOEC) measured in toxicity studies, and then applying an assessment factor (AF). The AF is a safety factor that accounts for uncertainties and variability in strength of the dataset. For antibiotics, a PNEC is additionally determined based on the minimum inhibition concentration and is referred to as the PNEC MIC (see note 2 for further details on PNEC derivation, and selection of the appropriate PNEC).

PNECs established by the AMRIA shall be used.

NOTE *If a compound specific PNEC is not listed, the default PNEC established by the AMRIA can be used in the absence of data. PNEC ENVs can be developed through standardized laboratory studies (e.g. OECD) and by applying assessment factors in a manner consistent with ECHA REACH guidance [7].*

NOTE 1 *Compound specific and default PNECs are available from the AMR Industry Alliance (<https://www.amrindustryalliance.org/wp-content/uploads/2022/04/AMR-Table-1-Update-February-2022.pdf>).*

NOTE 2 *Approaches to reduce AMR risk in the environment are still under development and various options are presented in peer reviewed literature [8], [9], [10], [11]. As the science progresses, PNEC values deemed to be protective against the spread of AMR might change.*

4.5 Control of routine discharges

4.5.1 General

The user shall reduce the antibiotics discharged to the environment to an RQ less than 1 (RQ <1) by employing good management practices and by applying a hierarchy of control.

NOTE *Annex A provides guidance for risk mitigation.*

4.5.2 Good management practices

API discharges to wastewater shall be minimized through review of the applicability of each of the following, including use, as determined by the review:

- a) products shall not be directly discharged to wastewater; reject batches that cannot be recovered or reworked shall be collected for treatment on-site or off-site;
- b) maximize use of closed transfers between process equipment to minimize spills;
- c) maximize equipment dry cleaning (vacuum, wipe) before wet cleaning; and
- d) collect any dry spilled material from floors and walls before washing an area down.

The review of applicability of good practices shall be documented and include a rationale for decisions made.

4.5.3 Hierarchy of control

Good management practices alone might not reduce API releases to an acceptable level. When further action is required (i.e. $RQ > 1$), API release reduction hierarchy, in accordance with 4.5.3.1 to 4.5.3.3 shall be applied.

4.5.3.1 Reduce losses to wastewater

To reduce losses to wastewater, the user shall:

- 1) evaluate process changes that could increase yields and reduce losses;
- 2) enhance equipment dry cleaning practices; and
- 3) redirect high API waste streams to solvent recovery, other treatment, or incineration.

4.5.3.2 Collect wastewater at point of generation (POG)

Specific waste streams that can be collected and treated on-site or off-site shall be identified.

Options for treating wastewater at source or POG shall be taken into account by:

- a) collecting and treating (e.g. oxidation or incineration) equipment cleaning rinses;
- b) collecting and then evaporating to reduce amount to be treated, thereby reducing treatment costs; and
- c) collecting and treating to destroy or separate and then destroy API, e.g. alkaline hydrolysis, advanced treatment and oxidation processes (such as ozone, ultraviolet, hydrogen peroxide, Fenton's, carbon adsorption, electrochemical oxidation, or combination of technologies).

4.5.3.3 Enhance existing wastewater treatment plant

Enhanced wastewater treatment shall be taken into account after all reduction efforts have been employed and when there are multiple waste streams requiring enhanced control. Options for enhancing wastewater treatment shall include:

- 1) optimizing API reduction performance through conventional operating parameter analysis and improvement;
- 2) improving biological solids separation through, e.g. membrane bioreactor; and
- 3) providing tertiary treatment (e.g. ozone, ultraviolet, hydrogen peroxide, Fenton's, carbon adsorption, electrochemical oxidation, membrane technologies or any suitable proven technologies).

4.6 Control of non-routine discharges

The user shall minimize the release of non-routine antibiotic discharges to the environment, including spills, application of treated wastewater to land for irrigation and firewater run-off containment, such as:

- a) spills/releases: process and storage areas (e.g. tanks, container storage areas, and process sewer systems) shall be designed, constructed and operated to prevent spills or releases to the environment. Containment system design and operation records shall be readily available; and
- b) irrigation with treated wastewater: risk assessments shall be conducted to determine potential risk from application to land (i.e. through run-off to surface water or leaching to groundwater, as well as to soil) and risks mitigated if RQ is more than 1 (RQ >1).

5.0 Solids management program

COMMENTARY ON CLAUSE 5

The level of detail and complexity of the environmental management system varies depending on compliance obligations and the nature of activities, including environmental aspects and associated environmental impacts. Compliance obligations can arise from mandatory requirements, such as applicable laws and regulations, or voluntary commitments, such as organizational and industry standards, contractual relationships, codes of practice and agreements with community groups or non-governmental organizations.

5.1 General

Solid waste containing antibiotic residues shall be managed on-site and off-site.

NOTE *Solid waste includes process waste, fermentation biomass and wastewater treatment sludge or solid residues generated from other pollution control measures.*

5.2 On-site management

The user shall demonstrate and check controls are in place for effective and safe handling, movement, storage, recycling, reuse and disposal of antibiotic waste.

The user shall have systems in place to prevent and mitigate accidental spills and releases to the environment. In the case of unpermitted or accidental release of antibiotic waste in the environment, remedial measures shall be in place to prevent reoccurrence and address associated environmental impacts.

Waste shall be stored such that discharges and unsafe conditions are prevented, and in accordance with applicable regulatory requirements:

- a) waste containers shall be labelled with contents, hazard characteristics (e.g. flammable, biological), and closed once waste is placed in the container;
- b) material shall be stored in quantities not exceeding the capacity of spill containment and shall be sheltered from weather/elements;
- c) spill containment integrity shall be inspected, documented and maintained in a satisfactory condition to prevent the discharge of waste materials into the environment;
- d) solid wastes shall be stored to prevent discharge as a result of rain/storm water run off;
- e) biomass from fermentation shall be managed to prevent environmental pollution;

- f) waste containers shall be in good condition and compatible with the materials being stored (e.g. free from corrosion, dents, bulges or other impairment that would impact adequate containment) and remain closed except during filling and emptying operations; and
- g) materials shall be stored to prevent events resulting from undesired reactions, incompatibilities, decomposition and/or self-ignition.

NOTE *Attention is drawn to regulatory requirements with regard to storage of waste.*

5.3 Off-site disposal

The user shall incinerate or dispose of solid waste containing antibiotic residue to a secure landfill site.

The user shall require the operator to confirm the landfill site is secure, designed and operated to prevent release into the environment.

NOTE *Land application of treatment plant sludges generated on-site is not preferred, however it can be used if the user demonstrates that the risk to soil and groundwater from leaching, and the risk to surface water from run-off is acceptable (RQ <1).*

The user shall verify documentation from each waste disposal contractor that:

- 1) waste disposal contractors possess authorizations/certifications from regulatory authorities to manage specific waste streams in accordance with local regulations;
- 2) any accidental spills and releases are reported to applicable authorities in accordance with regulatory and/or permit requirements; and
- 3) records (e.g. waste/classification determinations, including analytical results, letters from waste contractors, and certificates of destruction) are maintained.

6.0 Management of change

Previous risk evaluation(s) shall be reviewed and updated when significant changes to operations are planned to determine whether the change impacts prioritization or mitigation strategies.

Significant changes shall include new antibiotics processed in the facility and modifications to existing processes (i.e. increase or decrease in use or discharge of antibiotics from operations), as well as changes to a relevant PNEC.

NOTE *Annex B provides guidance for auditing.*

Annex A (INFORMATIVE)

Guidance for risk minimization

A.1 Risk reduction

Risks should be prioritized and potential mitigation options for those identified to be most significant should be implemented.

A.2 Process improvements

Process improvements to increase and/or optimize the overall yield, such as modernization of the process should be monitored to prevent or minimize the upstream antibiotic load. Process improvements should not be made if they conflict with good manufacturing practice (GMP) requirements.

A.3 Minimize API loss

Cleaning procedures should be optimized to reduce the antibiotic loading and to lower disposal costs by performing a thorough initial dry cleaning and by reducing the volume of high strength rinses being generated. An additional separate cleaning step (pre-rinsing) should be undertaken to remove large portions of APIs from large volume wash waters. The high load pre rinse streams can be separated and addressed subsequently by a selective technology or incineration/thermal oxidation.

NOTE *If dry cleaning is performed, workplace safety should be carefully monitored. Dry cleaning should not be an option if cleaning in place (CIP) is mandatory, according to the company's standard operating procedure (SOP).*

A.4 Segregate/collection waste

Mass balances can also aid in identifying wastewater stream(s) that should be segregated for disposal at an off-site facility, waste streams suitable for effective on-site treatment prior to disposal, and waste streams that require specific pre-treatment prior to disposal to a wastewater treatment system.

Analyses should be conducted to determine whether any residuals pose a risk either to a subsequent WWTP (e.g. inhibition or interference) or to a receiving environment (i.e. lake, river, or ocean) after discharge. To avoid high loads of antibiotics entering a site's wastewater influent, the user should retain good knowledge of the content of antibiotics in waste streams. Waste stream analysis can allow manufacturers to potentially optimize and implement the most effective pollution prevention and control measures.

A.5 Assess alternatives to discharging

Antibiotic removal is compound specific and should be addressed on a case-by-case basis. Mass transfer processes (antibiotics trapping) can be employed to remove antibiotics from solution into the solid phase, thereby concentrating the volume of waste for treatment.

NOTE 1 *Activated carbon adsorption, chemical precipitation or flocculation, membrane separation or thermal processes (evaporation) generate either concentrated liquids or solids (for incineration).*

NOTE 2 *Removal efficiencies of different treatments vary with different antibiotics, depending on the suitability of the treatment for the antibiotics and on the specific wastewater composition in each case (e.g. salinity, turbidity, organic load).*

A.6 WWTP modifications/improvements

COMMENTARY ON CLAUSE A.6

Many facilities in API production and final dosage production in the pharmaceutical industry rely on the use of neutralization, equalization, and physical/biological (primarily activated sludge) treatment technologies for their wastewater treatment. However, many antibiotics are only partially removed in conventional biological treatment because of their physical and chemical characteristics.

More advanced technologies, such as ozonation or electrochemical oxidation (e.g. Fenton's reagent) can be applied at manufacturing sites to remove specific compounds for which conventional treatment approaches do not work.

NOTE *End-of-pipe treatment is an alternative, although this option is not preferred due to higher volumes, mixing with other chemicals, and lower concentrations of the compound to be treated.*

A.7 Pre-treatment options

In certain cases, wastewaters could be investigated in more detail for the possibility of physico-chemical pre-treatment. In order to verify the destruction or removal of antibiotics, such investigations should encompass physical removal through precipitation, flocculation or adsorption to activated charcoal or other substrates, possibly furthering hydrolysis through raising or lowering the pH, with or without additionally heating the wastewater, or ozonation. Additionally, treatment with UV radiation, or advanced oxidation processes (AOPs) using UV with photosensitisers or oxidizers could be tested.

Best Available Techniques (BAT) Reference Documents (BREFs) can be consulted for pre treatment options for wastewaters from the chemical sector [12], [13]. Pre-treatment options and case studies are also found in the literature [12], [14], [15], [16], [17].

NOTE *Examples for pre-treatment options were also presented by the Pharmaceutical Supply Chain Initiative (PSCI), including:*

- a. in the course of a PSCI sponsored webinar on how to manage APIs in manufacturing effluent (Part 3) which took place on 25th October 2016 (<https://pscinitiative.org/resource?resource=297>);*
- b. in the course of the PiE/AMR Deep Dive training seminar held on 17th September 2019 in Hyderabad, India (<https://pscinitiative.org/resource?resource=482>).*

The user should be aware that any kind of pre-treatment will generate additional costs, including environmental costs (e.g. increased energy consumption, additional raw materials consumed, more CO₂ produced, or other kinds of wastes generated).

Wastewater incineration should be the last option, as an inordinate amount of energy is needed to evaporate water, often constituting well over 98% of a wastewater, to eventually combust the minor residues of recalcitrant or (eco)toxic organics.

Annex B (INFORMATIVE)

Program auditing

To check that internal and external antibiotics manufacturing facilities within the supply chain minimize the risk of ABR developing through the release (intentional or accidental) of antibiotics into the environment, on-site internal EHS audits and audits of external suppliers should be performed.

Audit antibiotic suppliers at least once every five years or when significant changes to operations or production volume are planned/occur in order to confirm adherence to this antibiotic manufacturing standard. Audits could be performed more frequently based on result of previous audits or discovery of heightened risk at the facility.

Focus should be on areas for environmental management, including water management, solid waste management, such as fermentation residues, spill prevention and response, chemical storage and handling, and employee training.

Audits should include a review of applicable regulatory requirements and permit conditions, the facility's environmental risk assessment of antibiotic discharges (quantified by mass balance or measurement, including validation documents following records retention) and assessed against PNECs.

Maintenance plans (for critical equipment and environmental controls) and incident investigation logs [corrective and preventative actions plan (CAPA)] for relevant incidents should be reported and included in the audit, as well as evaluating supplier practices for evaluating their own supply chain, waste and wastewater disposal records.

Audits should include evaluation of any antibiotic mass balance performed, local dilution factors selected and/or any sampling and analysis methodology used to verify adherence to the PNEC.

Facility tours should assess operating conditions to verify practices are in place and are being followed, as required (while in-person facility tours are preferred over remote auditing, certain circumstances may mean carefully planned, virtual auditing may be necessary).

The facility tour should include:

- a) antibiotic manufacturing areas;
- b) storm water collection and retention practices and/or systems;
- c) on-site wastewater treatment plant(s) (WWTP);
- d) waste storage areas, process and domestic wastewater collection and treatment;
- e) deep wells, underground and above-ground storage tanks with associated visible piping;
- f) fuel storage locations;

- g) solvent storage and recovery;
- h) warehouses other physical storage sheds/locations
- i) external tours of the facility including discharge locations (where safely accessible);
- j) pollution control devices; and
- k) receiving stream identification and observation, and fire water retention.

Audit reports should identify any non-conformity to the standard, and highlight any gaps, deficiencies, or deviations (e.g. from generally accepted industry practices and/or contractual commitments and communicated expectations related to antibiotics discharges).

NOTE *Audit reports remain confidential between the company and the supplier or manufacturing site, subject to the audit unless the supplier or manufacturing site agree otherwise). Companies could opt to publicly report, for example, aggregate audit information as part of their overall EHS program reporting.*

Users should also follow up with the supplier (facility) to develop acceptable action plans for recommendations from the audit. The supplier's performance should be monitored to confirm progress of actions, including subsequent remedial action closure consistent with specified timelines. Results and ongoing appropriateness of suppliers should be monitored.

ANNEX C (INFORMATIVE)

Case study examples

C.1

CASE STUDY:

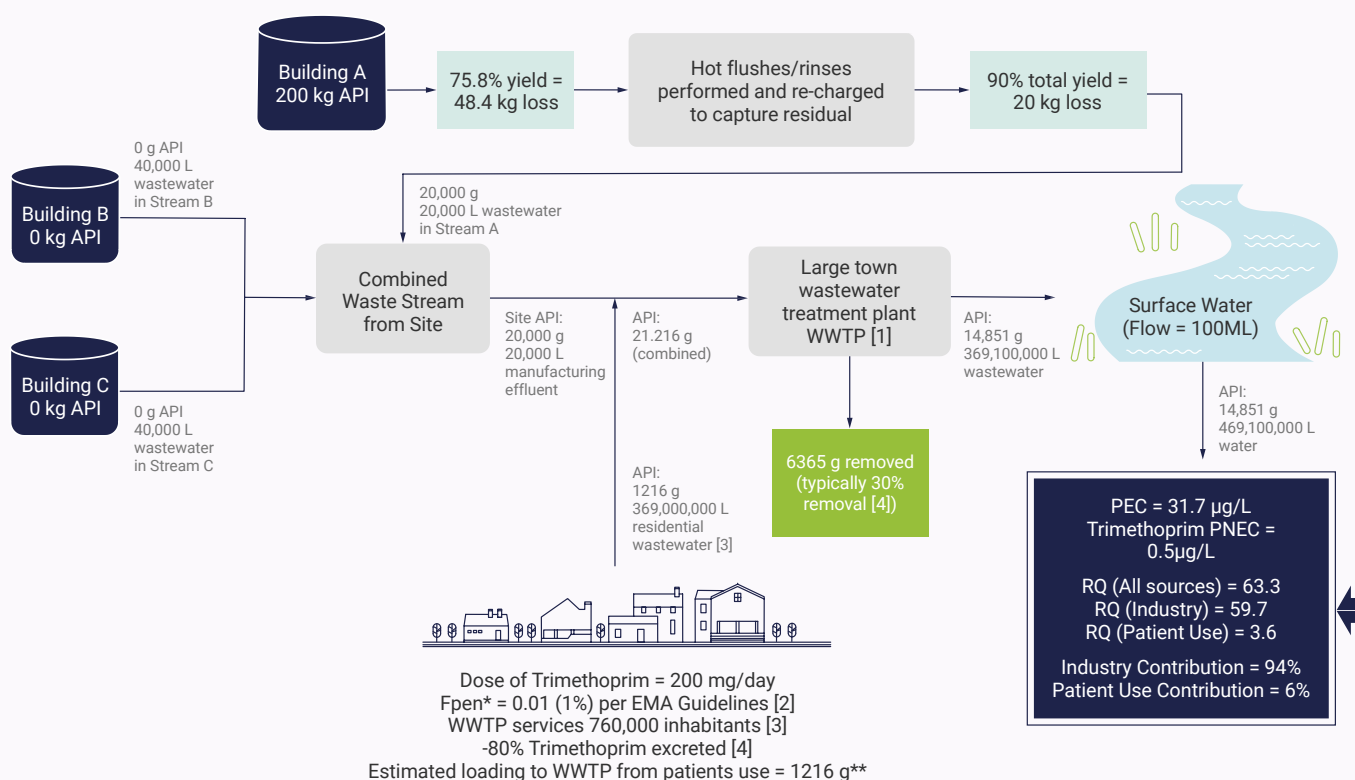
Manufacturing of Trimethoprim (without on-site treatment/controls) losses are too high

Figure C.1 illustrates industry contribution of 20 kg is too high for the surface water concentration to be below PNEC RQ = 59.7, and therefore this example would not conform to the standard.

The manufacturer shall reduce losses to meet PNEC so the RQ is less than 1 (RQ<1).

Figure C.1

Manufacturing of Trimethoprim (without on-site treatment/controls) losses are too high



NOTE 1 *How to read this diagram:*

1. *Building A: 200 kg typical batchsize;*
2. *75.8% yield following first processing steps:*
 - a. *remaining antibiotic as residual in filter dryers, equipment, etc.*
3. *Hot rinses/flushes are done of the equipment in an attempt to capture remaining antibiotic and increase overall yield:*
 - a. *after flushes, yield increases to approximately 90%; and*
 - b. *estimated loss of 20 kg (high but from an actual scenario) Building A effluent;*
4. *Antibiotic in the waste stream is combined from all buildings and whole manufacturing effluent sent for off-site treatment:*
 - a. *combined with municipal waste (e.g. patient use);*
5. *For trimethoprim, studies have shown an average of 30% removal in standard wastewater treatment (4).*
6. *Treated effluent discharged into surface water.*

- NOTE 2
1. *The article provides evidence for selection of multi-resistant E. coli from hospital effluent-ScienceDirect*
 2. *ERA: http://ema.europa.eu/en/documents/scientific-guideline-environmental-risk-assessment-medicinal-products-human-use-first-version_en.pdf*
 3. *A complete mass balance for plastics in a wastewater treatment plant—Macroplastics contributes more than microplastics—ScienceDirect.*
 4. *An Environmental Risk Assessment for Human-Use Trimethoprim in European Surface Waters—PubMed (nih.gov).*

* *F_{pen} = Fraction of population receiving drug*

** *Patient Use (g) = [Dose (mg/day) * # inhab * F_{pen} * % excretion] / 1 000 g.*

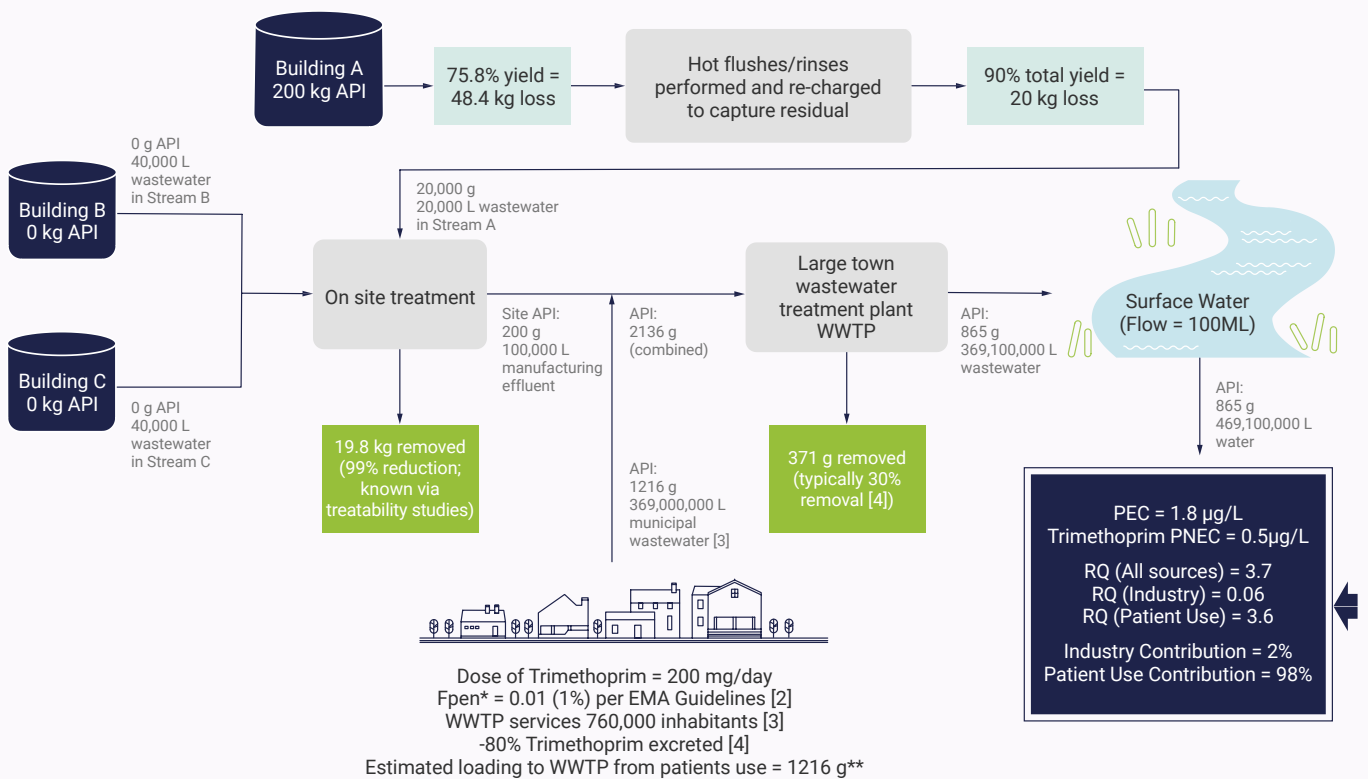
C.2

CASE STUDY: Manufacturing of Trimethoprim (on-site treatment/controls)

Figure C.2 showcases industry contribution where 20 kg is acceptable in the surface water because the concentration is below the PNEC, i.e. the RQ is less than 1 (RQ = 0.6), and therefore would conform to the standard.

Figure C.2

Manufacturing of Trimethoprim(on-site treatment/controls)



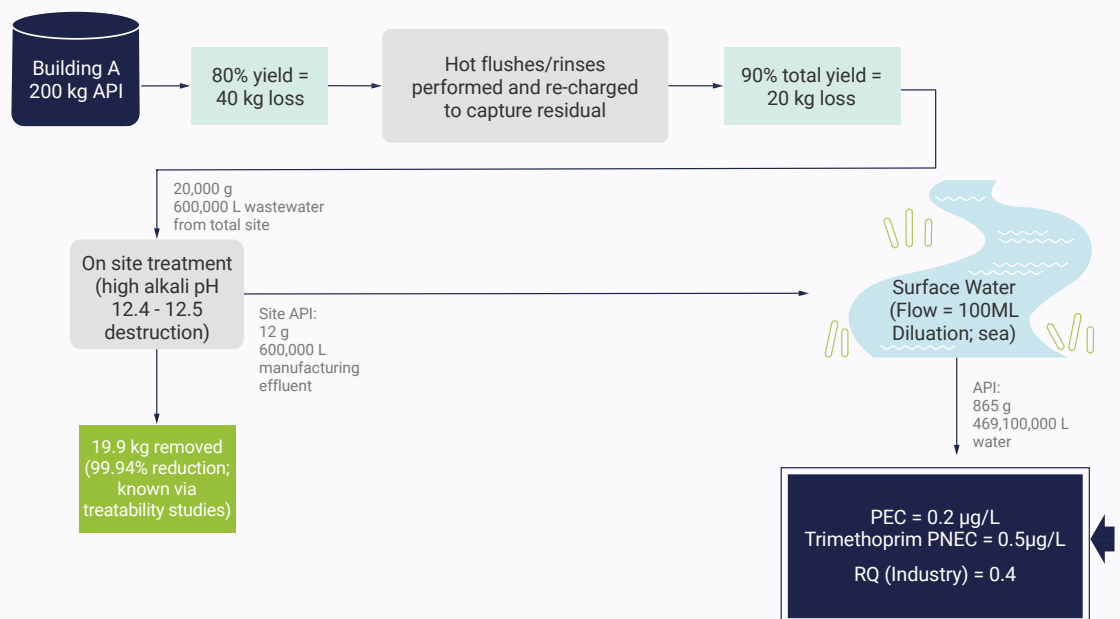
C.3

CASE STUDY: Manufacturing of Trimethoprim (direct discharge: on-site treatment/controls)

Figure C.3 provides an example where industry contribution of 20 kg acceptable in the surface water because the concentration is below the PNEC, i.e. RQ is less than 1 (RQ = 0.4), and therefore would conform to the standard.

Figure C.3

Manufacturing of Trimethoprim (direct discharge: on-site treatment/controls)



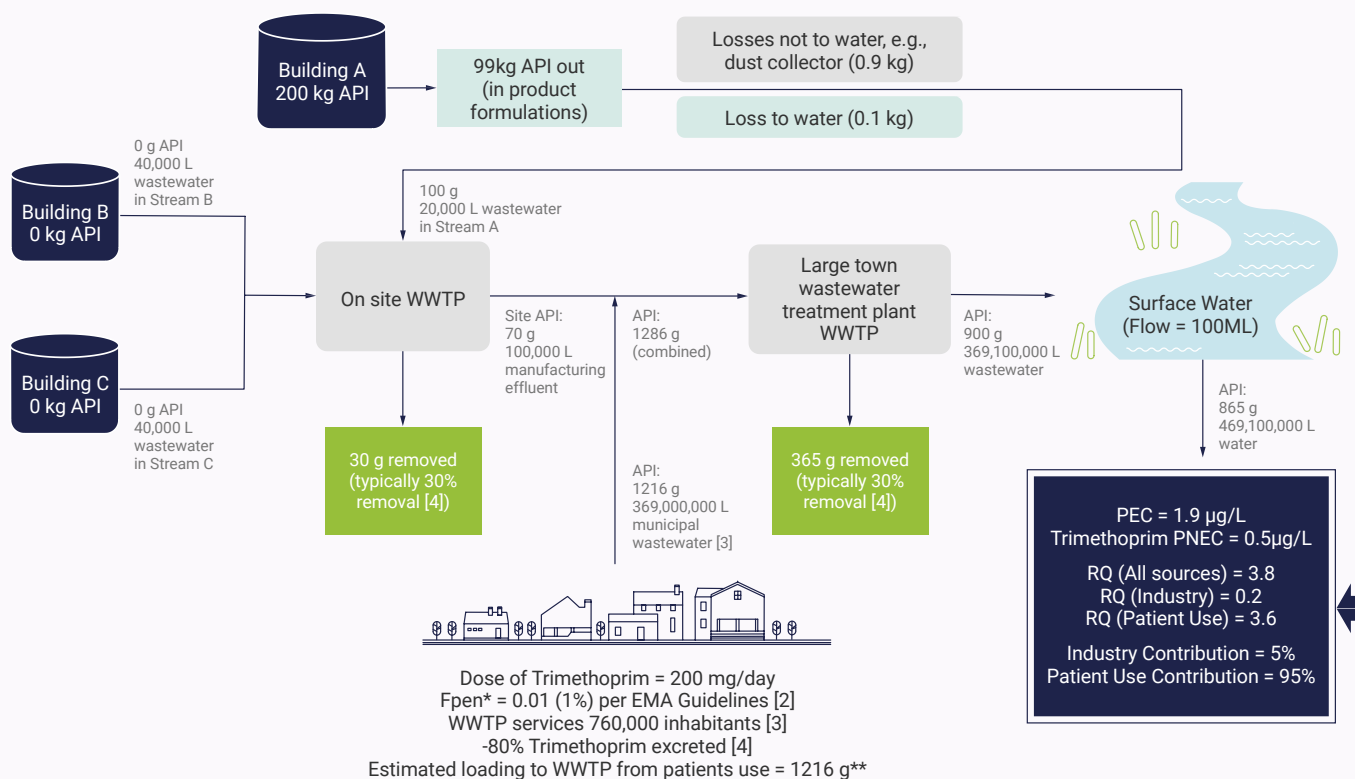
C.4

CASE STUDY: Tableting of Trimethoprim

Figure C.4 provides an example where a contribution of 20 kg is acceptable in the surface water because the concentration is below the PNEC, i.e. RQ is less than 1 (RQ = 0.2), and therefore would conform to the standard.

Figure C.4

Tableting of Trimethoprim



NOTE

1. This article provides evidence for selection of multi-resistant *E. coli* by hospital effluent—ScienceDirect
2. Environmental Risk Assessment: http://ema.europa.eu/en/documents/scientific-guideline-environmental-risk-assessment-medicinal-products-human-use-first-version_en.pdf
3. A complete mass balance for plastics in a wastewater treatment plant—Macroplastics contributes more than microplastics—ScienceDirect
4. An Environmental Risk Assessment for Human-Use Trimethoprim in European Surface Waters PubMed (nih.gov)

* F_{pen} = Fraction of population receiving drug

** Patient Use (g) = [Dose (mg/day) * # inhab * F_{pen} * % excretion] / 1000 g

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About The AMR Industry Alliance

The AMR Industry Alliance is a coalition of over 100 biotechnology, diagnostic, generics and research-based biopharmaceutical companies and trade associations that was formed to drive and measure industry progress to curb antimicrobial resistance. As the largest life-sciences coalition of its kind, the Alliance aims to provide sustainable solutions in the fight against AMR through broad industry momentum, public-private collaboration and multi-sectoral action.

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