Antibiotic manufacturing standard

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

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amr INDUSTRY ALLIANCE
UNITED AGAINST ANTIMICROBIAL RESISTANCE

Updated May 2025

Authors' note: This standard was updated based on approximately two years of antibiotic manufacturers' implementation experience, publication of the World Health Organization guidance aimed at controlling manufacturing emissions from antibiotic manufacturing (September 2024), and, in the case of the AMRIA antibiotic predicted no-effect concentrations (PNECs) referenced in the Standard, additional scientific information and/or analysis.

Case studies (C1-C4) were updated in September 2022 to better clarify the data and to correct numeric errors. No material changes in the overall outcome of any case study resulted from the updates.

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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] [2].

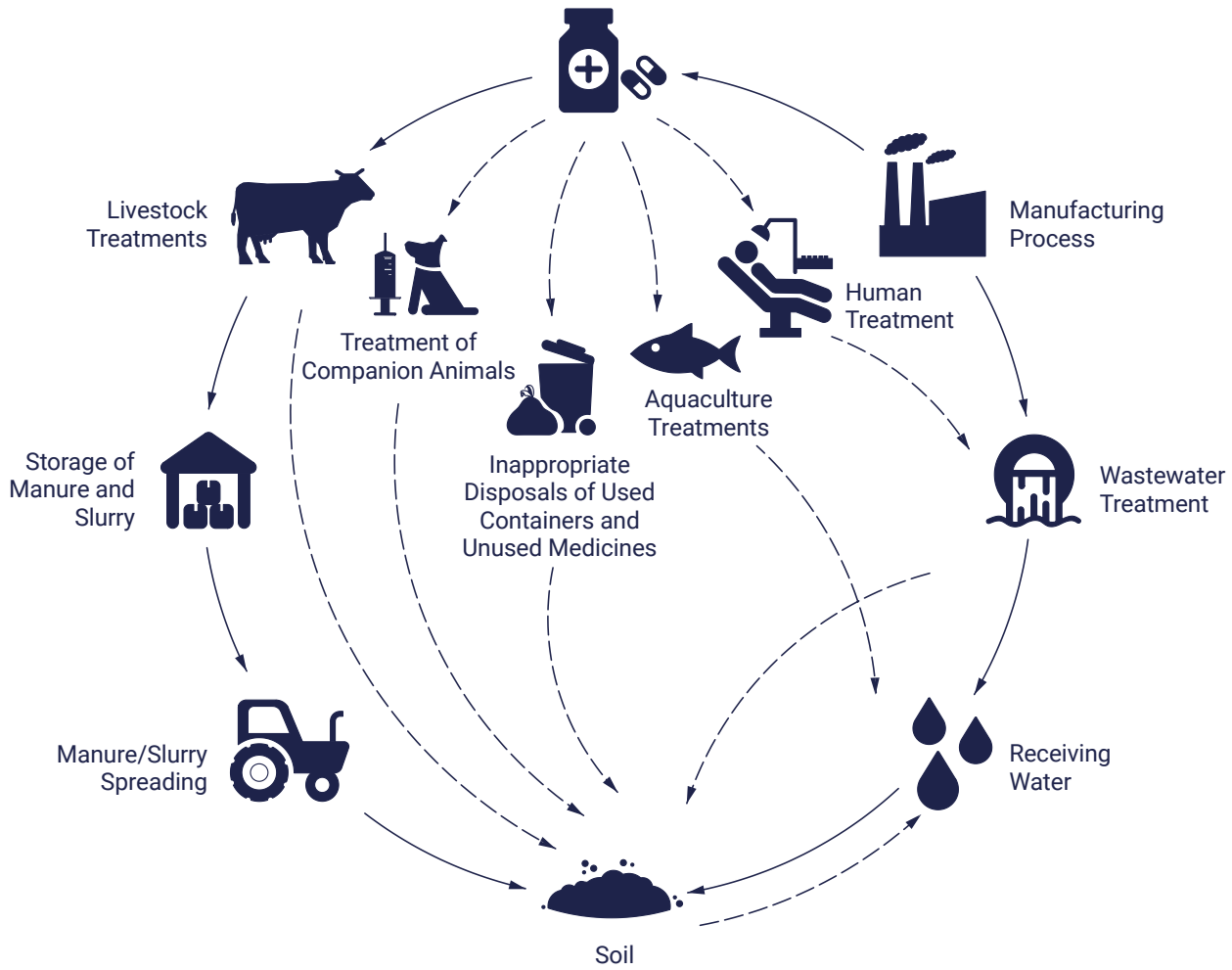
There are several causes of ABR, including over and misuse of antibiotics in human and animal health in the agriculture and aquaculture sectors. Human health is inextricably linked to environmental health and as such there are concerns that the presence of antibiotics in the environment may also contribute 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 volume 5(12) [3].

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 [4] 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.

0.4 Other guidance

In 2024, the World Health Organization (WHO) published non-binding guidance titled "Guidance on Wastewater and Solid Waste Management for Manufacturing of Antibiotics" [5] directed at a broad range of stakeholders, including industry. The WHO, in their guidance, acknowledges significant similarities with the AMRIA standard, while noting some differences.

0.5 Certification against this standard

An organization that seeks to demonstrate manufacture of an antibiotic(s) at a specific manufacturing location that meets the requirements of this standard may seek independent third-party certification.

The British Standards Institution (BSI) has developed an accompanying certification scheme "BSI Kitemark™ for Minimized Risk of Antimicrobial Resistance Certification" [6]. The BSI has been determined by the AMRIA to be a suitably qualified organization, deploying suitably qualified and competent assessor(s) to undertake audits against the requirements of this standard and to issue certificates of conformance to this 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.

The standard covers all steps from the manufacturing of active pharmaceutical ingredients (APIs) and formulation into finished products, including primary packaging.

The standard applies to both liquid and solid waste with a focus on liquid effluent, run-off and discharges to land. Risk assessment within the standard covers risks for the selection of resistance by antibiotics and (in the case of fermentation and sludge generated from wastewater treatment) release of resistant bacteria.

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-eco-toxicity 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 wild type organisms

3.1.6 common effluent treatment plant

a facility to treat industrial effluent from more than one industrial unit (e.g. pharmaceutical manufacturing site), as permitted by national and/or local regulation

NOTE *CETPs are typically found in India and are distinct from municipal wastewater treatment plants.*

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

3.1.7 effluent

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

3.1.8 manufacturing

processes which create medicines

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

3.1.9 minimum inhibitory concentration

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

3.1.10 pharmaceuticals in the environment

presence of pharmaceuticals in environmental compartments

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

3.1.11 point of generation

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

3.1.12 predicted environmental concentration

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

3.1.13 predicted no-effect concentration

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

3.1.14 receiving water

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

3.1.15 risk quotient

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

3.1.16 secure landfill

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

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

3.1.17 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

3.1.18 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.*

3.1.19 zero liquid discharge

wastewater management system for the maximum recovery of water from wastewater; recovered water beneficially reused (e.g. in boilers, cooling towers) and not released to environment (e.g. not used for irrigation).

Salts and other solids removed from the wastewater are properly disposed of 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
CETP	common effluent treatment plant
MEC	measured environmental concentration
MIC	minimum inhibitory 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:

PEC / PNEC = Risk Quotient (RQ)
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.

Estimation and measurement of antibiotic concentrations

Concentrations of antibiotics in effluents can be determined either through mass balance calculation based on calculated or estimated losses during production [7] or measured through chemical analysis of wastewater samples [8] [9]. A mass balance based on measured process yields and losses is a conservative approach that, when conducted using representative process information, should provide estimates equal to or more than the actual concentration in the target point of measurement.

Mass balance is a management system tool for identifying potential antibiotic losses throughout the manufacturing process. Except where limited in application by this standard, or, in circumstances for which the rationale not to perform a mass balance is justified and documented (e.g. filling API into glass vials and all spills/washings are collected, sampled and analyzed), losses from manufacturing processes (including primary packaging) should be determined by mass balance and actions identified

and implemented to minimize the loss of antibiotic into the environment (and notwithstanding the requirement to ensure the concentration of antibiotic at the end of the mixing zone in the receiving aquatic environment is below the PNEC).

Whilst mass balance methods can often be applied to formulation processes, they may be more limited for chemical synthesis processes and fermentation-based processes. Mass balance estimates cannot be applied for liquid run-off since it is not a closed system.

The conservative approach for a mass balance calculation for synthetic API production is to assume 100% reaction efficiency (on a stoichiometric basis) of well-defined masses of reactants. However, most often reaction efficiencies are lower than 100%. To take into account lower than 100% (the default), the manufacturer should provide transparent data on reaction efficiencies, ensuring that these are not underestimated [5].

For fermentation-based manufacturing steps, the API mass generated by the microorganisms, corresponding to the “mass in”, is difficult to assess. Chemical mass determination of APIs generated by fermentation is therefore needed [5].

Chemical analysis may also have limitations. Chemical analysis only reflects concentrations at the time point of sampling (which may not reflect the average concentration period nor the peak concentration period), and chemical analysis methods may not be available or readily developed at the required level of quantification for all antibiotics.

For fermentation-based processes: use of tertiary or advanced treatment processes known to effectively reduce heterotrophic bacteria or characterization of wastewater to confirm absence of process microorganism or resistance genes is required. For other processes: avoid microbial treatment of wastewater with antibiotic concentrations far in excess of PNECs if possible (refer to section 4.4.1 release of resistant bacteria). If applied, disinfection may be used subject to regulator/permit conditions and other risk considerations.

The rationale for selection and use of specified treatment technology should be documented and correct installation and application should be verified though operational monitoring and internal audit.

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 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 applicable water balances, sampling and chemical analysis data, process flow diagrams and criteria for allowable discharge to wastewater shall be maintained and made readily available.

Guidance on wastewater treatment technologies is available from the Pharmaceutical Supply Chain Initiative (PSCI) [10].

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 or equal to 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 RQ, which is a comparison of the predicted environmental concentration (PEC) or measured environmental concentration (MEC) of an API in the environment resulting from a site's wastewater discharge to the predicted no-effect concentration (PNEC).

Production waste streams containing antibiotic residues may be managed on-site and/or treated on-site and/or off-site to reduce antibiotic concentrations (and/or for other reasons). The API mass lost to process wastewater should be divided by the total volume of wastewater generated from the facility for one day (24 hours) of the batch process period to estimate the antibiotic concentration.

NOTE *Annex C (case study examples) illustrates.*

For an off-site WWTP, if the measured volume of wastewater treated daily by the treatment plant is known, this may be used to calculate the concentration in the treatment plant influent. If the volume is not known, or, to simplify the calculation, a standard dilution factor of 10 may be applied to the manufacturing plant discharge to calculate the concentration in the influent of the treatment plant. Optional chemical analysis or models can account for removal within the treatment plant to calculate the concentration in the effluent of the treatment plant. Additional dilution is applied in the receiving water based on Section 4.4.2e.

For an off-site CETP, calculation of dilution within the treatment plant (using known volumes or standard dilution factors) is not allowed. Optional chemical analysis can account for removal within the treatment plant to calculate the concentration in the effluent of the treatment plant. Additional dilution is applied in the receiving water based on Section 4.4.2e.

Liquid effluent: antibiotic-resistant bacteria

Discharges of antibiotic-resistant bacteria and resistance genes in the wastewater may also pose a health risk. Antibiotics present at concentrations above the PNEC-res in untreated wastewater or in the microbial culture of fermentation-based processes may select for and drive resistance before wastewater is released. Hence, removal of resistant bacteria prior to release in addition to meeting PNECs for antibiotics (see Section 4.4.3) should be considered. For fermentation-based processes, there is often no feasible alternative to microbiological waste treatment. Pretreatment of fermentative antibiotic production wastewater to remove antimicrobials, e.g. through enhanced hydrolysis, is the best way to reduce risks for resistance development.

Such manufacturing facilities should have tertiary or advanced treatment processes (e.g. oxidative treatment, ultraviolet [UV] light, chlorination, sterile filtration, thermal treatment) capable of efficient reduction of heterotrophic bacteria (in addition to the removal achieved through biological treatment) prior to release of liquid effluent into sewers or water bodies, or characterisation of wastewater performed to demonstrate absence of process microorganism or resistance genes.

Discharge to Land

Where wastewater is discharged to soil or for horticultural use (including water from ZLD processes, which by definition would not strictly be “ZLD”), a risk assessment must be performed and controls applied to ensure discharged water meets the PNEC as assessed by mass balance or chemical analysis. Salts and other solids removed from the wastewater should be properly disposed of in a manner which does not allow release to water (e.g. incineration, contained landfill).

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 (for guidance on dilution factors see [11]). These factors are often site-specific and depend on API characteristics, waste-water 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) [7].*

b) analytical testing: analytical testing is not required, however testing waste streams for antibiotic residue may be undertaken to supplement the mass balance calculations or may be used to determine the antibiotic concentration at the site end-of-pipe;

c) whenever analytical testing is performed: 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) [8], Stanway (9), and Caldwell, et al., 2016 [12].*

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%;

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: local dilution factors or standard dilution factors may be used.

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. Standard dilution factors (i.e. 10 for a river, 100 for an ocean discharge) may be used unless it can be established doing so would result in an underestimation of the PEC (e.g. if discharge is to a very low flow river).

Dilution factors for emissions into a lake should be assessed on a case-by-case basis and the rationale for the dilution factor used documented.

NOTE 4 *Standard dilution factors are not available for emissions to lakes due to very large variability in lake volumes.*

NOTE 5 *Where readily available, mixing factors established by a regulatory agency (or agencies) for a receiver water (river, ocean or lake) may be used.*

NOTE 6 *Environmental models are available, which can be used to calculate the dilution of the discharged effluent (e.g. CORMIX).*

NOTE 7 *Guidance for estimating dilution factors is available from the Pharmaceutical Supply Chain Initiative (PSCI) [11].*

4.4.3 Predicted no-effect concentration (PNEC)

The PNEC is the concentration of a chemical in the environment at which minimal impact is expected.

A number of approaches have been published for determining threshold concentrations of antibiotics that are not likely to select for resistance (PNEC-res) in the environment [13]. However, there is currently no standardized, widely accepted method for determining PNEC-res values in receiving water environs. While the AMRIA in this standard and the WHO in their guidance [5] use PNECs derived from minimum inhibitory concentration (MIC) distribution data (e.g. from the EUCAST database) to inform environmental risk assessment, as the science progresses, PNEC values deemed to minimize the risk of AMR development in the environment might change.

The AMR Industry Alliance has published and maintains a table of antibiotic PNECs, including PNEC-MIC values and the PNEC-Environment (PNEC-ENV) values (see note to this section). Both PNEC-ENV and PNEC-MIC values are important parameters relevant for water quality. PNEC-ENV values, derived from ecotoxicology data, are intended to be protective of ecosystem services. PNEC-MIC values, derived from minimum inhibitory concentration data, are intended to minimize the risk of resistance selection.

When available, the lowest of the two PNEC values (PNEC-ENV and PNEC-MIC) established by the AMRIA shall be used to inform an antibiotic manufacturing emission risk assessment. At this time, the PNEC-MIC value is adopted as the best-available proxy to mitigate the risk of resistance promotion; therefore, if no compound-specific PNEC-MIC value is available, a default PNEC-MIC of 0.05 µg/L, based on a statistical analysis of available data, is included in the table. If an antibiotic is not listed in the table, read-across from an antibiotic in the same class (based on similar chemical structure, mode of action, and antibacterial activity) may be made to determine a PNEC-MIC [14]. Alternatively, a default PNEC of 0.05 µg/L shall be applied in the absence of PNEC-MIC data.

PNECs established by the AMRIA shall be used. These PNECs are derived following the recommendations in the WHO Guideline [5]; the PNECs for resistance were derived according to the methodology of Bengtsson-Palme & Larsson, from standardized MIC data available in the EUCAST database.

NOTE *Compound specific and default PNECs are available from the AMR Industry Alliance together with explanatory introductory text (https://www.amrindustryalliance.org/wp-content/uploads /UPDATED-Table-1-AMRIA-Sept-2026.pdf).*

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 providing tertiary treatment (e.g. ozone, ultraviolet, hydrogen peroxide, Fenton's, carbon adsorption, electrochemical oxidation, membrane technologies or any suitable proven technologies). Examples of pre-treatment technologies are available from PSCI [10].

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 that 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 and sludge shall be treated by incineration or disposed to secure landfill or managed as indicted in the following paragraphs to prevent environmental pollution;

f) for fermentation-based processes, unless waste is incinerated, treatment achieving ≥ 99%* API removal (e.g. through enhanced hydrolysis, chemical or enzymatic treatment), should be used since relatively large quantities of solid or semi-solid waste (fermentation residue) may be produced, which may contain relatively high antibiotic concentrations.

**Treatment achieving <99% API removal shall be justified in a documented risk assessment.*

g) Unless solid waste from a manufacturing site or a third party CETP is to be incinerated), treatment achieving ≥ 80%* API removal should be achieved by use of an appropriate technology, with justification for the use and effectives of the technology documented

**Treatment achieving <80% API removal shall be justified in a documented risk assessment.*

h) 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

i) 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. In some jurisdictions, internationally recognized hazardous waste labelling is not allowed; local requirements must be adhered to.*

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 low- er 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 is mandatory, according to the company's standard operating procedure.*

A.4 Segregation/collection of 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-treat- ment 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 [15], [16]. Pre-treatment options and case studies are also found in the literature [15], [17], [18], [19], [20].

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, 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 three 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, ongoing corrective action planning implementation, or discovery of heightened risk at the facility. The rational for an audit frequency greater than three years must be documented.

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, all dilution factors used (local, standard, wastewater treatment, receiving water) 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.

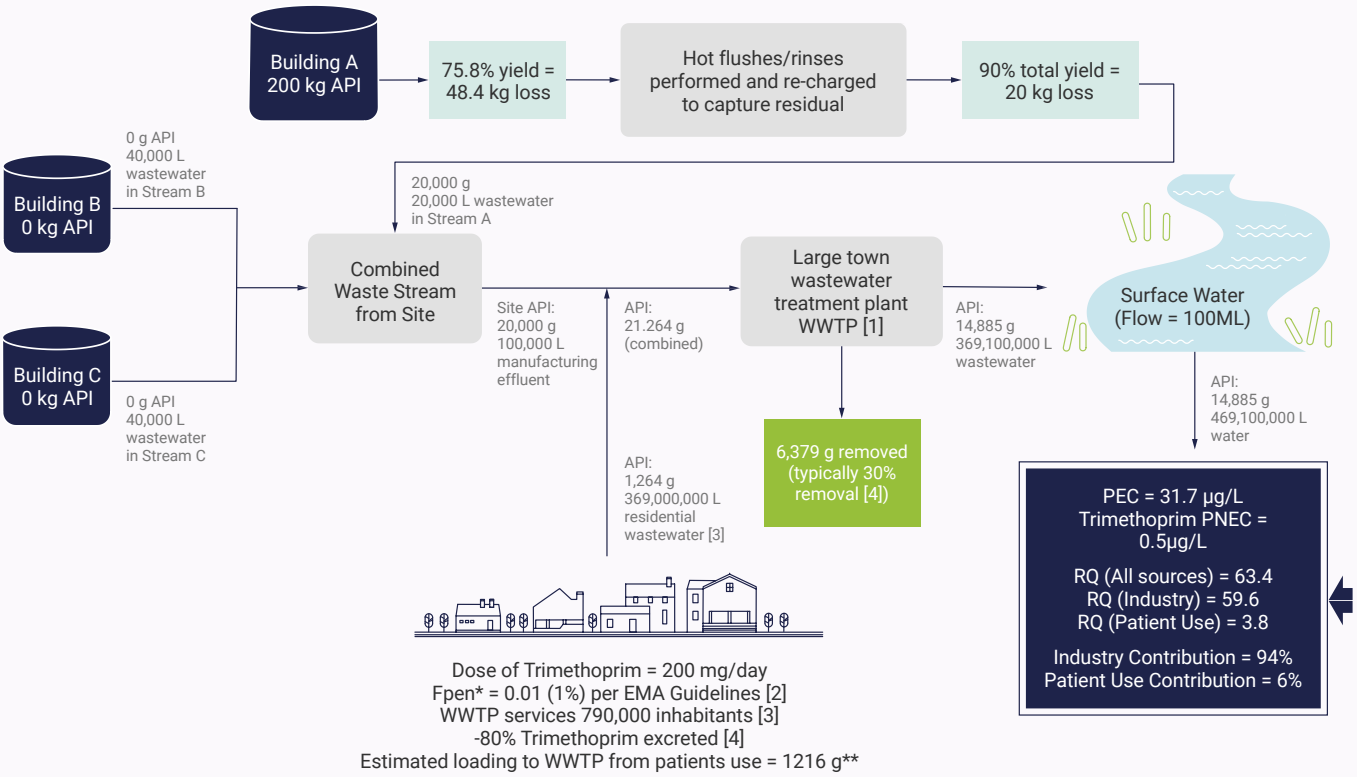
ANNEX C (INFORMATIVE) Case study examples

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 *Mass losses and wastewater volumes are on a daily basis.*

NOTE 2 *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 3

1. *The article provides evidence for selection of multi-resistant E. coli from hospital effluent: https://www.sciencedirect.com/science/article/pii/S0160412021000611*
2. *ERA: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-environmental-risk-assessment-medicinal-products-human-use-revision-1_en.pdf*
3. *A complete mass balance for plastics in a wastewater treatment plant— Macroplastics contributes more than microplastics: https://www.sciencedirect.com/science/article/pii/S0043135421005054*
4. *An Environmental Risk Assessment for Human-Use Trimethoprim in European Surface Waters: https://pmc.ncbi.nlm.nih.gov/articles/PMC4790302/*

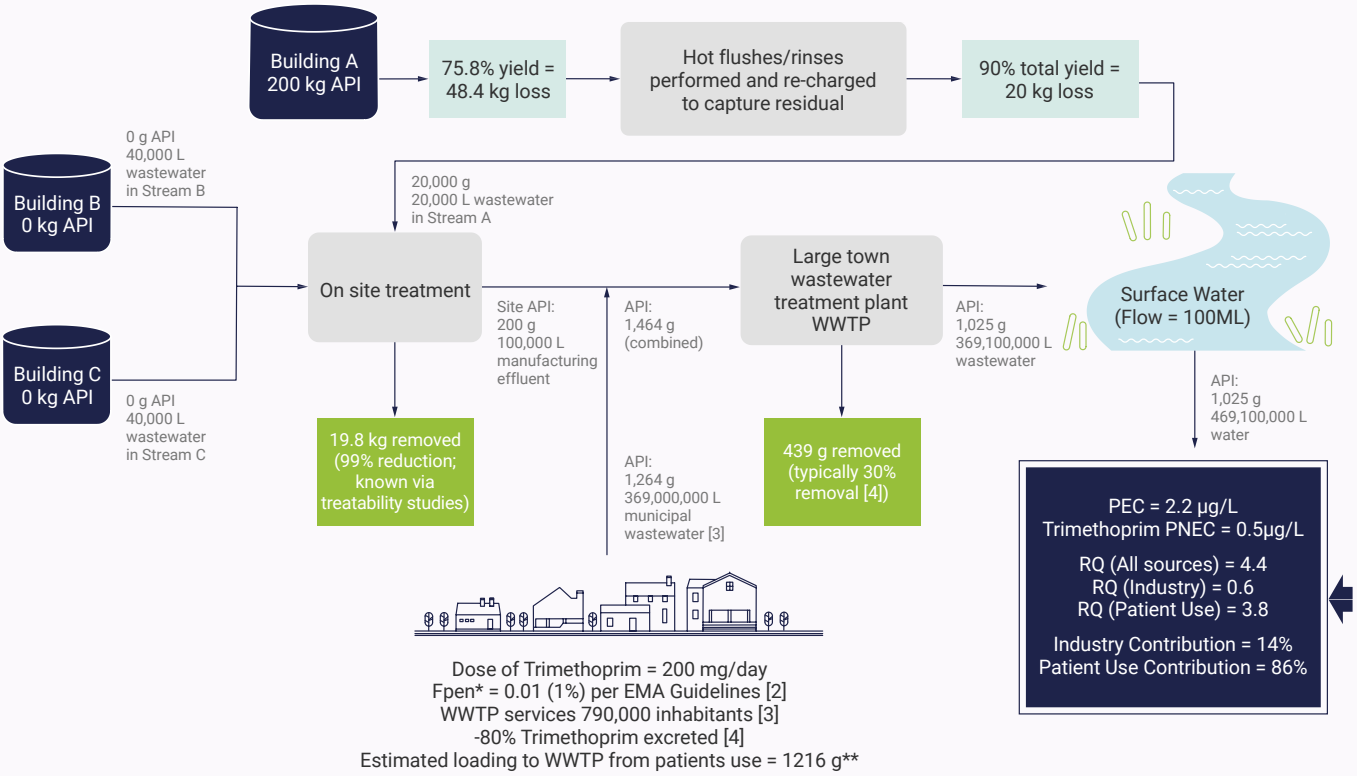
* *Fpen = Fraction of population receiving drug*

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

C.2 CASE STUDY: Manufacturing of Trimethoprim (on-site treatment/controls)

Figure C.2 provides an example where an industry loss of 20 kg is acceptable because waste stream treatment and dilution results in a concentration in the receiving body (surface water) below the PNEC.

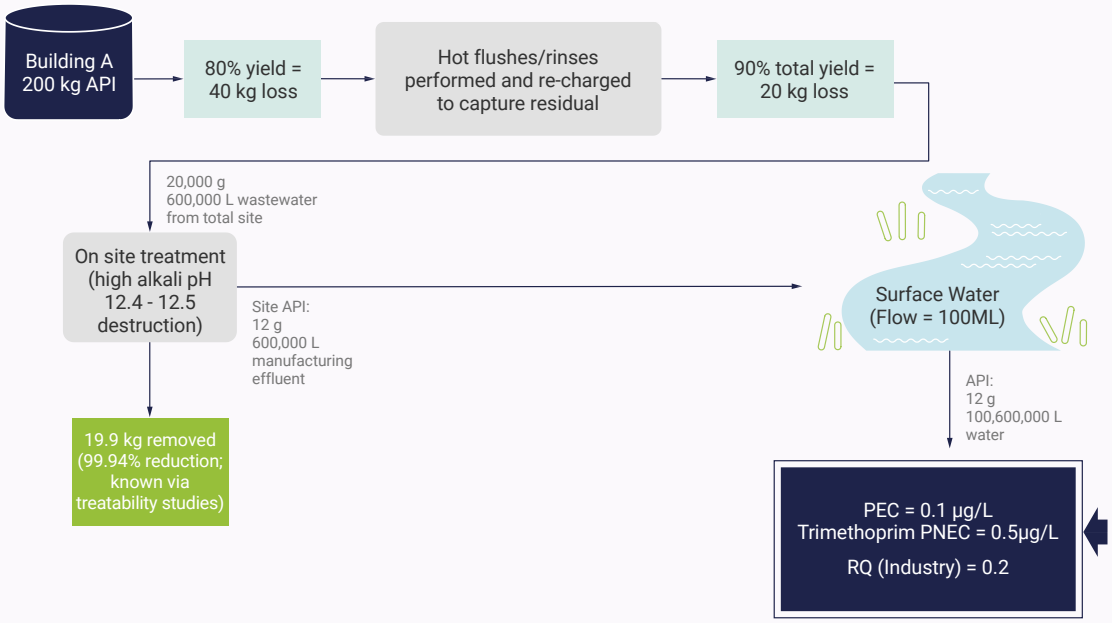
Figure C.2 Manufacturing of Trimethoprim(on-site treatment/controls)



C.3 CASE STUDY: Manufacturing of Trimethoprim (direct discharge: on-site treatment/controls)

Figure C.3 provides an example where an industry loss of 20 kg is acceptable because waste stream treatment and dilution results in a concentration in the receiving body (surface water) below the PNEC.

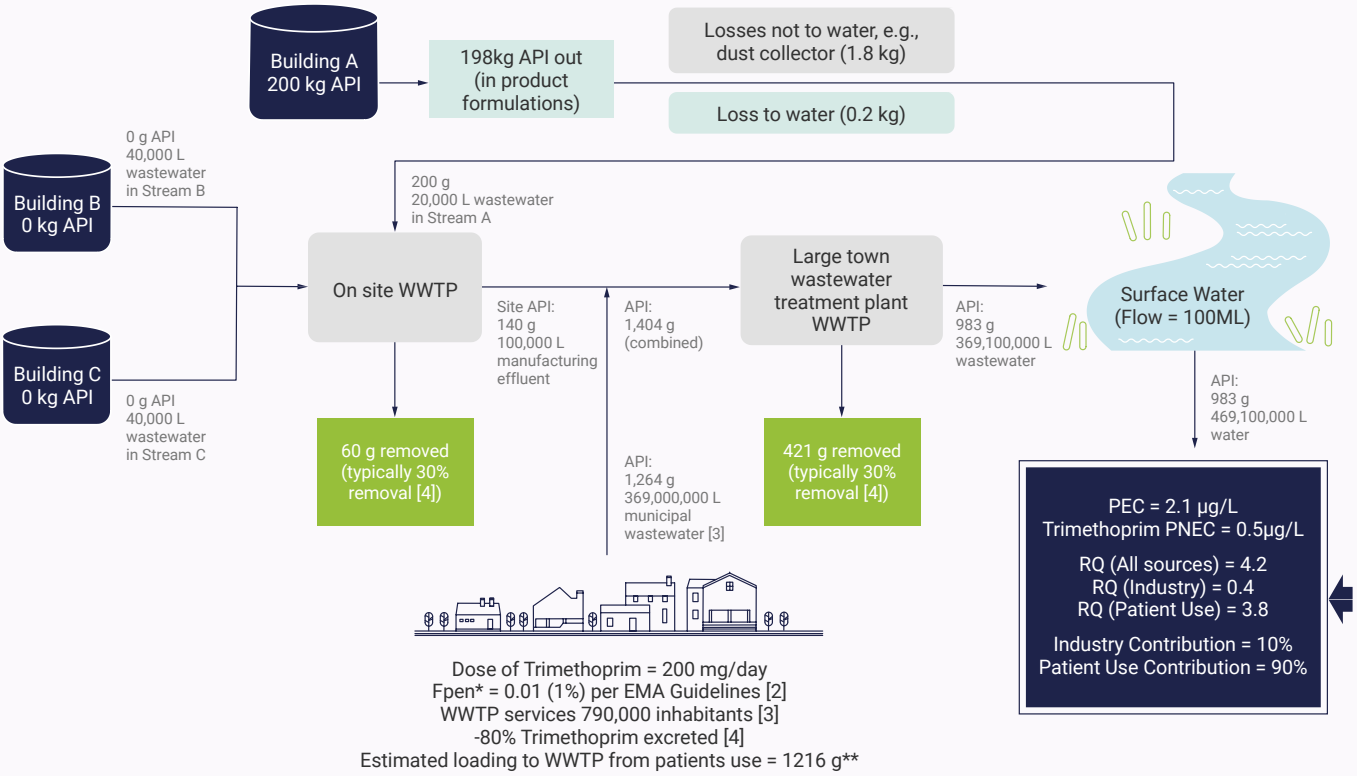
Figure C.3 Manufacturing of Trimethoprim (direct discharge: on-site treatment/controls)



C.4 CASE STUDY: Tableting of Trimethoprim

Figure C.4 provides an example where an industry loss of 20 kg is acceptable because waste stream treatment and dilution results in a concentration in the receiving body (surface water) below the PNEC.

Figure C.4 Tableting of Trimethoprim



NOTE

1. *This article provides evidence for selection of multi-resistant E. coli by hospital effluent: https://www.sciencedirect.com/science/article/pii/S0160412021000611*
2. *Environmental Risk Assessment: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-environmental-risk-assessment-medicinal-products-human-use-revision-1_en.pdf*
3. *A complete mass balance for plastics in a wastewater treatment plant—Macroplastics contributes more than microplastics: https://www.sciencedirect.com/science/article/pii/S0043135421005054*
4. *An Environmental Risk Assessment for Human-Use Trimethoprim in European Surface Waters PubMed: https://pmc.ncbi.nlm.nih.gov/articles/PMC4790302/*

* *Fpen = Fraction of population receiving drug*

** *Patient Use (g) = [Dose (mg/day) * # inhab *Fpen * % 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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