# Annex 6

## Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance

# 1. Introduction and scope

## 1.1 Background

According to research by UN Environment (*1*), growing antimicrobial resistance (AMR) linked to the discharge of drugs and particular chemicals into the environment is one of the most worrying health threats of today. AMR accounts for an estimated 700 000 deaths per year worldwide and, by 2030, will represent up to US$ 3.4 trillion in gross domestic product (GDP) loss (*2*). AMR has been identified as a priority at the World Health Assembly since 1998 (*3*), with rising momentum throughout the years. Since 1998, there have been a series of World Health Assembly resolutions on AMR. These paved the way to the Sixty-eighth World Health Assembly in May 2015, where the World Health Assembly endorsed a global action plan to tackle AMR, including antibiotic resistance, the most urgent drug resistance trend (*4*). More recently, the *Thirteenth General Programme of Work (2019–2023)* highlighted the need to address this emerging threat, under the section for "Tackling antimicrobial resistance" (*2*). It is only recently that the need to address waste and wastewater management from pharmaceutical production has been explicitly addressed. Namely, on 30 November 2018, the World Health Organization's (WHO's) Executive Board meeting decided that technical input will be provided to good manufacturing practices (GMP) guidance on waste and wastewater management from the production of critically important antimicrobials (*5*, *6*). The present *Points to consider* document was written further to this recent decision.

We are entering a post-antibiotic era, where simple and previously treatable bacterial infections can kill and where routine medical procedures that rely on antibiotic preventative treatment, such as joint replacements and chemotherapy, will not be possible. The 2014 O'Neill report commissioned by the Government of the United Kingdom of Great Britain and Northern Ireland estimated that antimicrobial-resistant infections may become the leading cause of death globally by 2050 (*7*).

The environment plays an important role in antimicrobial resistance. Microorganisms in soil, rivers and seawater can develop resistance through contact with resistant microbes (transfer of resistance genes), antibiotics and disinfectant agents released by human activity (*1*), as well as heavy metals (*8*, *9*) that may propagate AMR in the environment. People and livestock could then be exposed to more resistant bacteria through food, water and air (*1*).

Pharmaceuticals entering the environment from industrial manufacturing activities are not the major source of antimicrobial resistance, but in countries that contribute the most to the production of antimicrobials, this issue can be significant. The levels of pollution with antimicrobials have been measured in waters in the proximity of pharmaceutical production facilities. Antimicrobial

concentrations in some effluents are too low to be lethal to exposed bacteria but may still be sufficient to induce antimicrobial resistance (*1*, *10*), but high concentrations have been found downstream of antimicrobial manufacturing sites in several countries. Scientific literature reports a correlation between the type and number of highly resistant bacteria and the level of antimicrobial pollution (*10*). This led to manufacturing sites being identified as one of the hot spots for development of AMR, but this knowledge dates from only a few years ago (*11*).

Poor control of waste (solid[1] or liquid) and wastewater, such as that encountered in some of the countries that are major global producers of pharmaceuticals, can often lead to the entry of antimicrobials into waters that are contaminated with pathogenic bacteria from untreated sewage. This increases the risk of development of AMR. Furthermore, a vast array of contaminants in municipal and industrial wastewater increases pressure on bacteria to become resistant (*1*, *11*). Eventually, from the passage of the production cycle to the effluent pipe, antimicrobial molecules (precursors and by-products) turn from valuable medicine to hazardous waste that has an impact on the efficacy of the product as well as human health and the environment.

Concentrations in river water depend on wastewater treatment facilities, as well as antimicrobial use in the populations they serve. Treatment plants are generally designed to remove conventional pollutants such as nutrients, organic matter, suspended solids and pathogens, but not pharmaceuticals such as antimicrobial agents (*1*). The level of treatment of manufacturing effluents or pharmaceutical waste (solid or liquid) can vary significantly, resulting in the necessity for municipal wastewater treatment plants to handle the waste. However, the activated waste may up-concentrate some antimicrobial agents, as well as antimicrobial-resistant bacteria, increasing the risk for AMR in environments where the sludge is applied. Recent evidence indicates the presence of a selection pressure for AMR within environments receiving wastewater from antimicrobial manufacturing, as opposed to environments receiving wastewater from municipal sewage treatment plants (*12*) that do not receive waste from antimicrobial manufacturing.

It is therefore important to significantly reduce the concentration of antimicrobials prior to disposal into the environment. However, the recommended approach in the absence of established standards would be to apply the precautionary principle, i.e. to not emit any waste until there is proof that the discharge does not have an adverse effect on human health or the environment.

[1] Solid waste is also considered in this document because, if not properly disposed of, different types of solid waste may leach into the surrounding environment and contaminate effluents.

Several initiatives have already been put in place by the United Nations (*13*, *14*), WHO (*4*), nongovernmental institutions (*15–17*), governments (*18–24*) and the industry itself (*25–29*). Industry should be committed to caring for the environment, and responsible manufacturing is encouraged by taking steps to minimize the environmental impact of operations and products, while also balancing the need to produce high-quality, life-saving medication.

This document is to be considered as a time-limited document that addresses the current needs for guidance on how GMP should be implemented to waste and wastewater management for production of antimicrobials. It leverages on the existing GMP and makes reference to relevant literature rather than containing detailed instructions. This document may be updated in the future, as the knowledge about suitable technologies on how to remove antimicrobial residues is expected to increase within the next few years and the requirements may be modified/adapted in consequence.

## 1.2 Purpose

The purpose of this document is to:

- provide recommendations and expectations for manufacturing facilities for medicines regarding waste management, to mitigate/prevent potential antimicrobial resistance;
- raise awareness of medicines' manufacturers, national regulatory authorities (NRAs) and especially GMP inspectorates and inspectors in all Member States, on sections of relevant GMP guidance that are applicable to the management of waste/wastewater from the production of antimicrobials, while emphasizing the importance of all aspects of GMP implementation and considering the parts of GMP that may not have a direct impact on product quality; and
- provide clarification on the interpretation of those clauses and specific measures that should be taken to be considered compliant with the relevant sections of GMP guidance, without changing the scope of GMP.

This document is not intended to cover AMR issues that are related to the human or veterinary use of antimicrobials or to other types of environmental contamination (*1*), such as the excretion of antimicrobials during their use. It should not be considered to provide exhaustive information on methods that can be used to control and reduce contamination of the environment with antimicrobials and related chemicals, such as active precursors or by-products coming from pharmaceutical production processes. It should also not be considered to provide information on the levels of antimicrobial residues that are considered acceptable.

### 1.3 Target audience

This document is targeted to:

- all pharmaceutical manufacturers engaging in synthesis and/or production of antimicrobials (primarily manufacturing sites for active pharmaceutical ingredients [APIs] and, secondly, manufacturing sites for finished pharmaceutical products [FPPs]);
- GMP inspectors and inspectorates from national medicines regulatory authorities;
- regulatory bodies that are responsible for enforcing environmental protection standards and waste/wastewater management in all Member States – consistent with a multidisciplinary approach, including but not limited to ministries of health, ministries of environment or pollution control boards, and ministries of agriculture, as appropriate; and
- waste and wastewater management services that handle antimicrobial waste and/or process effluents from the pharmaceutical industry.

## 2. Glossary

The definitions given below apply to the terms as used in this guideline that are not defined in existing WHO terms and definitions databases. They may have different meanings in other contexts.

**active pharmaceutical ingredient (API).** Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure and function of the body.

**antimicrobial resistance (AMR).** Antibiotic resistance develops when bacteria adapt and grow in the presence of antibiotics. The development of resistance is linked to how often antibiotics are used. Because many antibiotics belong to the same class of medicines, resistance to one specific antibiotic agent can lead to resistance to a whole related class. Resistance that develops in one organism or location can also spread rapidly and unpredictably through, for instance, the exchange of genetic material between different bacteria, and can affect antibiotic treatment of a wide range of infections and diseases. Drug-resistant bacteria can circulate in populations of human beings and animals, through food, water and the environment, and transmission is influenced by trade, travel and both human and animal migration. Resistant bacteria can be found in food, animals

and food products destined for consumption by humans. Some of these features also apply to medicines that are used to treat viral, parasitic and fungal diseases, hence the broader term antimicrobial resistance.

**finished pharmaceutical product (FPP).** A finished dosage form of a pharmaceutical product that has undergone all stages of manufacture, including packaging in its final container and labelling.

## 3. Review of the environmental aspects of good manufacturing practices

GMP are, a priori, intended to control the manufacture of medicines, and in principle do not focus on the environmental aspects of these. However, GMP include many aspects related to the protection of the environment and workers. If fully implemented, GMP should therefore prevent many different types of waste from contaminating the environment.

Given that the lack of control in the downstream processes of manufacturing medicines will ultimately lead to their loss in efficacy, we may no longer focus only on the aspects of GMP that are directly linked to the quality of medicines. Medicines that are no longer effective lose their value and it is therefore crucial for manufacturers and all stakeholders to take action in order to protect the efficacy of those medicines. Only one major class of antibiotics has been discovered since 1987 (*30*) and too few antibacterial agents are in development to meet the challenge of multidrug resistance (*4*).

The *WHO good manufacturing practices for pharmaceutical products: main principles* (*31*) and *WHO good manufacturing principles for active pharmaceutical ingredients* (*32*) contain a limited set of clauses related to environmental issues. Waste and wastewater management are addressed only briefly. The following clauses are the only ones considered to be of relevance:

> ***WHO good manufacturing practices for pharmaceutical products: main principles. Annex 2, WHO Technical Report Series, No. 986, 2014 (31)***
>
> ***Waste materials***
>
> *14.44 Provisions should be made for the proper and safe storage of waste materials awaiting disposal. Toxic substances and flammable materials should be stored in suitably designed, separate, enclosed cupboards, as required by national legislation.*
>
> *14.45 Waste material should not be allowed to accumulate. It should be collected in suitable receptacles for removal to collection points*

*outside the buildings and disposed of safely and in a sanitary manner at regular and frequent intervals.*

***WHO good manufacturing practices for active pharmaceutical ingredients. Annex 2, WHO Technical Report Series, No. 957, 2010 (32)***

***4.6 Sewage and refuse***

*4.60 Sewage, refuse and other waste (e.g. solids, liquids or gaseous by-products from manufacturing) in and from buildings and the immediate surrounding area should be disposed of in a safe, timely and sanitary manner. Containers and/or pipes for waste material should be clearly identified.*

On the other hand, the *WHO good manufacturing practices for pharmaceutical products containing hazardous substances* (*33*) contains more detailed requirements regarding waste and wastewater management, which can be applied to the production of antimicrobials. These guidelines cover those hazardous substances traditionally belonging to reproductive health hormones and highly potent materials such as steroids or sensitizing medicines such as beta-lactam antibiotics. According to these guidelines, a hazardous substance or product is a "product or substance that may present a substantial risk of injury, to health or to the environment". As antimicrobials are deemed to present a substantial risk of injury to both health and the environment, when released into the environment through their action on microorganisms, they should be considered for inclusion in the scope of this guidance.

The following clause is considered to be of general relevance to the protection of the operators, the environment and the public:

***WHO good manufacturing practices for pharmaceutical products containing hazardous substances. Annex 3, WHO Technical Report Series, No. 957, 2010 (33)***

***General***

*2.1 Facilities should be designed and operated in accordance with the main GMP principles, as follows:*

- *to ensure quality of product;*
- *to protect the operators from possible harmful effects of products containing hazardous substances; and*
- *to protect the environment from contamination and thereby protect the public from possible harmful effects of products containing hazardous substances.*

The guidelines require risk assessments to determine the potential hazards to the operators and to the environment of hazardous substances contained in all types of waste, as per the following clauses:

> ***Risk assessment***
>
> *4.1 Not all products containing hazardous substances are equally potent and risk assessments should be carried out to determine the potential hazards to operators and to the environment. The risk assessment should also determine which phases of the product production and control cycles, from manufacture of the API to distribution of the finished product, would fall under the requirements of these guidelines. Risk assessments applicable to the environment should include airborne contamination as well as liquid effluent contamination.*
>
> *4.2 Assuming that the risk assessment determines that the products or materials being handled pose a risk to the operators and/or the public and/or the environment, the guidelines to be followed for the design and operation of the facility should be as detailed in this document.*

Such risk assessments should therefore be performed by manufacturers as required, in principle, for any substance deemed to be hazardous.

The guidance already has a requirement prohibiting discharge of hazardous substances into normal drainage systems:

> ***Environmental protection***
>
> *7.1 Due to the hazardous nature of the products being handled in the facility, neither the product nor its residues should be allowed to escape into the atmosphere or to be discharged directly to normal drainage systems.*

It also has a requirement for protection of the atmosphere and the public in the local vicinity:

> *7.2 The external atmosphere and the public in the vicinity of the facility should be protected from possible harm from hazardous substances.*

The above clause may be considered to apply to effluents and water streams near facilities, as their contamination with antimicrobials can have a public health impact. The literature contains several reports of effluents and water streams contaminated with potentially dangerous levels of antimicrobials (*8*, *10*, *12*).

The guidance also has a requirement for treatment of hazardous effluent before it is discharged:

> *7.3 If liquid effluent poses a safety or contamination risk, the effluent should be treated before being discharged to a municipal drain.*

However, it should be noted that the municipal drain may not be suitable to handle the large quantities of hazardous effluents such as those that are released by large pharmaceutical companies, and therefore manufacturers are requested to carefully consider this in their approach.

The guidance also contains a general statement about handling of liquid and solid waste effluent and another about safe disposal:

> ***13. Effluent treatment***
>
> *13.1 Liquid and solid waste effluent should be handled in such a manner as not to present a risk of contamination to the product, personnel or to the environment.*
>
> *13.2 All effluent should be disposed of in a safe manner, and the means of disposal should be documented. Where external contractors are used for effluent disposal they should have certification authorizing them to handle and treat hazardous products.*

As per the above clause, where external contractors are used for effluent disposal, they should have certification authorizing them to handle and treat hazardous products.

The management of waste that is obtained from quality control testing in a laboratory setting at a manufacturer's site or contract laboratory is covered by the following clause:

> ***Guidance on good practices for pharmaceutical quality control laboratories. Annex 1, WHO Technical Report Series, No. 957, 2010 (34)***
>
> ***7. Premises***
>
> *7.6 Procedures should be in place for the safe removal of types of waste including toxic waste (chemical and biological), reagents, samples, solvents and air filters.*

The amount of antimicrobial waste being generated by laboratory testing activities is generally considered to be negligible compared to the amounts that are being generated by manufacturing activities but should still be considered in exceptional cases, e.g. if very large amounts of sample are being tested by a quality control laboratory.

## 4. Expectations for manufacturers of antimicrobials

Application of the requirements outlined in the above-mentioned GMP clauses shall be verified during onsite inspections. In addition, manufacturers of APIs and FPPs should consider retaining documentation on the following:

- a risk assessment for all contaminants related to antimicrobial manufacturing, in the event that they are released into the environment, and the associated risk of development of resistant microorganisms;
- based on the above risk assessment, waste-stream analysis for each antimicrobial agent produced (at API sites and FPP sites). This analysis should be repeated whenever there is a change in production affecting waste streams;
- the quantity and nature of the waste generated, including the analytical data and documentation of analyses performed and their findings on the levels of antimicrobial agents or their precursors;
- regular reports on the collection, treatment and disposal of waste and wastewater; the frequency should be risk-based and in line with local, regional or international regulatory requirements, as applicable;
- information on the methods used to treat the waste should be documented to be effective for each specific antimicrobial or antimicrobial precursor. Analytical data demonstrating the conversion of these substances and their residues to non-hazardous waste materials should be available at the facility and kept up to date;
- if effective waste treatment is not yet implemented for all waste streams resulting from the manufacture of each API or FPP, documentation on a time-limited strategy should be in place, with specified milestones for that implementation, specifying actions towards achieving treatment that significantly reduces the concentration of the antimicrobial substance or its precursor (and its microbial source, when relevant); and
- a rationale and risk assessment as to why the manufacturer selected specific methods of decontamination of manufacturing waste containing antimicrobials and/or their mitigation strategy. Many decontamination methods already exist that reduce or remove antimicrobials (and microbes that have produced fermentative antimicrobials) from waste streams entering the environment from antimicrobial manufacturing: secondary and tertiary wastewater treatment; membrane filtration and ozonation; and ultraviolet disinfection and heat treatment, which are even more effective at

removing viable bacteria (*1*, *11*). Incineration may also be considered for solid or semi-liquid waste. The zero-liquid effluent approach or zero-discharge policy is encouraged, especially when the risk is assessed to be high or unclear, as it prevents any contamination of the environment. The level of effectiveness and by-products should be considered when adopting a particular approach.

It is recommended that this documentation be maintained at the manufacturing facility regardless of whether or not an external contractor has been used. These points to consider should be used by manufacturers as part of their self-audits, in order to verify their continued level of GMP compliance. Although the aim is not to reduce verification of the quality of products, the waste management practices and related documentation listed in this *Points to consider* document could be reviewed and scrutinized during regulatory inspections.

It should be noted that the above requirements will not be used to draw a conclusion on the level of GMP compliance of a manufacturing site. Their purpose is to guide/encourage manufacturers to apply all of the GMP principles. The application of these principles will help to tackle the emergence of AMR, by raising awareness of the preventative measures that manufacturers should take to adequately manage the waste and wastewaters that are generated while manufacturing antimicrobials.

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