World Health Organization

Frequently asked questions to accompany the WHO Guidance on wastewater and waste management for manufacturing of antibiotics

June 2024

Why is the guidance needed?

Evidence indicates that in parts of the world where antibiotic manufacturing occurs, waste and wastewater from manufacturing antibiotics can contain high levels of active pharmaceutical ingredients (APIs), with antibacterial properties.[1] Insufficiently treated waste from manufacturing antibiotics is often discharged into waterways and soils. This means, large volumes and high concentrations of antimicrobial compounds may enter the environment where antibiotics are manufactured, or along the manufacturing chain.

While pollution from antibiotic manufacturing is unlikely to contribute significantly to the transmission of antibiotic resistance already widespread in society, manufacturing emissions present a major concern for the emergence of new resistance.[2] Such events are rarer than transmission events, but the consequence of emergence and subsequent spread of a new and successful resistance may be vast and global, with potential to undermine the effectiveness of antibiotics produced in those very same manufacturing facilities.

Currently, there is no independent guidance outlining targets and risk assessment approaches for the manufacturing of antibiotics. Therefore, this WHO-led guidance aims to address the gap by providing an independent scientific basis for inclusion of targets to prevent emergence and spread of antibiotic resistance in binding mechanisms and to outline best practice risk management approaches to achieve and verify targets.

Who should implement the guidance?

The target audiences for this guidance are:

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[1] Larsson DG. Pollution from drug manufacturing: review and perspectives. Philos Trans R Soc Lond B Biol Sci. 2014 Nov 19;369(1656):20130571.

[2] Larsson DGJ, Flach CF. Antibiotic resistance in the environment. Nat Rev Microbiol. 2022 May;20(5):257-269.

- regulatory bodies at the national or regional level responsible for the regulation of pharmaceutical product manufacturing or wastewater and solid waste specifically in countries or regions that manufacture and formulate antibiotics;
- procurers of antibiotics for both human, animal and plant use;
- entities responsible for generic substitution schemes and reimbursement decisions for antibiotics;
- third party inspectors and auditors, and;
- industrial actors in all stages of the antibiotic production chain, from initial manufacturing to final commercial formulation
- investors in the antibiotic manufacturing sector.
- waste and wastewater management services that handle antibiotic waste

Other audiences may also have interest in this guidance including researchers, physicians, veterinarians and the general public.

What is the scope of this guidance?

This guidance focuses on all antibiotics intended for human, animal or plant use. The guidance covers all steps from the manufacturing of APIs and formulation into finished pharmaceutical products, including primary packaging.

Targets outlined in the guidance include human health-based targets for reduction of emergence and spread of antibiotic resistance, and ecotoxicological targets to reduce risks for aquatic life caused by antibiotics. Beyond outlining targets, the guidance also outlines a system for risk management to meet the proposed targets and for verification of such targets by internal and external audits.

There is a focus on liquid effluent – including piped effluent and site runoff (e.g., from storage sites of solid waste) and discharges to ground or groundwater. However, the guidance also covers solid waste performance targets and general procedures on management of solid waste contaminated by antibiotic agents.

The guidance outlines options for two levels of progressive improvement: good and stringent. It covers all waste streams, indicating how each waste stream can be assessed and how the associated risks of releasing antibiotics into the environment can be reduced to levels that are safe and are anticipated to not contribute to resistance development or ecotoxicity.

How does it differ from industry-led initiatives?

Industry-led initiatives have been moving forward to improve practices to address risks posed by waste and wastewater from manufacturing. This guidance acknowledges and builds on these efforts but recognizes the need to independently develop guidance to be used for regulatory activity such as inspections.

In addition, this guidance emphasises the need for a progressive implementation and improvement through the application of different instruments according to a two-level approach: good and stringent.

This guidance strongly emphasises the importance of public transparency across risk management and verification of results. Several technical aspects also differ, such as how and when mass-balance calculations can be used to assess emissions, including the requirement for chemical analyses in all fermentation-based production. Chemical analyses, rather than theoretical estimates, are also required to take into account removal of antibiotics during wastewater treatment. The guidance outlines the need to assess risks during peak emissions rather than averages. To meet the stringent level, this guidance specifies that the assessment of risks for selection of resistance must be using concentrations of antibiotics within the wastewater, before dilution, as bacteria present in the wastewater are also at risk for selection.

For Zero Liquid Discharge (ZLD) plants, the guidance outlines the need to perform an assessment of the risks associated with emissions to land/soil. There are also solid waste risks assessment approaches specified including run off from external storage sites and technology specifications for the release of resistant bacteria.

Notably, this guidance has been developed following the highest standards according to WHO rules of procedures and protocols to ensure transparency, independence and scientific credibility. The need to preserve access to medicines from sudden disruption of the supply chain has also been factored into the development of this document.

Why is this relevant for AMR?

Bacteria and bacterial genes move between humans, domestic animals and the environment. A One-Health approach to address AMR is endorsed widely by all UN agencies and by many other actors globally[3] The environment serves as a reservoir for new and existing resistance genes that, over time, reach bacteria . Therefore, selection pressures on resistance genes potentially induced by uncontrolled release of antibiotics into the environment, should be avoided.

Why is it only focused on antibiotic manufacturing?

The release of antimicrobial agents from their manufacturing into the environment can be harmful especially at high concentrations. Antibiotics are the focus of this guidance because current evidence is most robust for antibiotic manufacturing both in terms of

[3] WHO, FAO, OIE, UNEP. Strategic framework for collaboration on antimicrobial resistance – together for One Health. Geneva: World Health Organization, Food and Agriculture Organization of the United Nations and World Organization for Animal Health; 2022.

understanding the risks and the availability of data to set targets for risk management. It is possible to establish and refine antibiotic targets in effluent water i.e., Predicted No Effect Concentrations (PNECs) to minimize the development of resistance and in most cases the ecotoxicity. For other antimicrobials is not yet possible to establish PNECs.

Moreover, bacteria pathogenic and non-pathogenic possess the unique capability to transfer genetic material between each other, setting them apart from other microbes such as fungi, parasites and viruses. This ability to transfer genetic material poses specific risks, as pollution containing antibiotics can lead to the selection and development of resistance in any bacteria. Consequently, these genes can transfer to other bacteria with pathogenic potential.

Who has asked for this guidance?

The need for international evidence-based guidance on the management of waste from antimicrobial manufacturing to guide the target audience of this document has been identified by many international bodies and reports including but not limited to:

- Several World Health Assembly (WHA) resolutions on AMR that lead to the endorsement of the *Global Action plan to Tackle AMR* by the Sixty eighth WHA (WHO, 2015)[4];
- UNEP reports: *2016 Emerging Issues of Environmental Concern*[5] and 2017 *Frontiers 2017 Emerging Issues of Environmental Concern*[6]*;*
- 2018 WHO Executive Board meeting request to provide technical input from the good manufacturing practices (GMP) guidance on waste and wastewater management from the production of critically important antimicrobials (Executive Board 114 2018, WHO 2019)[7];
- Annex 6: Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance in: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fourth report. Geneva: World Health Organization; 2020 (WHO technical report series; no. 1025);
- The 2021 G7 Health Ministers' meeting communique (June 2021)[8];

[4] World Health Organization. (2015). Global action plan on antimicrobial resistance. Geneva. https://iris.who.int/handle/10665/

[5] UNEP (2016). UNEP Frontiers 2016 Report: Emerging Issues of Environmental Concern. United Nations Environment Programme, Nairobi.

[6] UNEP (2017). Frontiers 2017 Emerging Issues of Environmental Concern. United Nations Environment Programme, Nairobi.

[7] World Health Organization (2019). Executive Board meeting request to provide technical input from the good manufacturing practices (GMP) guidance on waste and wastewater management from the production of critically important antimicrobials (Executive Board 114 2018).

[8] https://www.gov.uk/government/publications/g7-health-ministers-meeting-june-2021-communique/g7-health-ministers-meeting-communique-oxford-4-june-2021

- AMR Global leaders group call to action: *Reducing Antimicrobial Discharges from Food Systems, Manufacturing Facilities and Human Health Systems into the Environment* (March 2022)[9];
- AMR Industry Alliance *Antibiotic Manufacturing Standard: Minimizing risk of developing antibiotic resistance and aquatic ecotoxicity in the environment resulting from the manufacturing of human antibiotics*[10];
- European Parliament's *Strategic approach to pharmaceuticals in the environment*[11];
- The International Federation of Pharmaceutical Manufacturers and Associations *Industry Roadmap for Progress on Combating Antimicrobial Resistance*[12];
- The O'Neill *Review on AMR: Antimicrobials in agriculture and the environment: reducing unnecessary waste*[13];
- *FAO, WOAH and WHO's Technical Brief on Water, Sanitation, Hygiene and Wastewater Management to Prevent Infections and Reduce the Spread of Antimicrobial Resistance*[14];
- *UNEP's Bracing for Superbugs: Strengthening environmental action in the One Health response to antimicrobial resistance*[15];
- Access to Medicines Foundation's Methods matter: What steps are companies taking to help curb AMR by manufacturing responsibly?[16]

Will the guidance have an impact on antibiotic supply and price?

Careful consideration has been paid to address potential impacts this guidance may have on antibiotic supply and price worldwide. The guidance outlines progressive improvement through a step-wise approach for manufacturers to achieve a

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[9] One Health Global Leaders Group on Antimicrobial Resistance (2022). Reducing Antimicrobial Discharges from Food Systems, Manufacturing Facilities and Human Health Systems into the Environment. Call to action by the Global Leaders Group on Antimicrobial Resistance. Geneva.
[10] AMR Industry Alliance (2022). Antibiotic Manufacturing Standard: Minimizing risk of developing antibiotic resistance and aquatic ecotoxicity in the environment resulting from the manufacturing of human antibiotics.
[11] European Parliament (2020). Strategic approach to pharmaceuticals in the environment'. https://www.europarl.europa.eu/doceo/document/TA-9-2020-0226_EN.html
[12] The International Federation of Pharmaceutical Manufacturers and Associations (2020) Industry Roadmap for Progress on Combating Antimicrobial Resistance. https://www.ifpma.org/publications/industry-roadmap-for-progress-on-combating-antimicrobial-resistance/
[13] O'Neill, J. (2015) Antimicrobials in Agriculture and the Environment: Reducing Unnecessary Use and Waste. The Review on Antimicrobial Resistance, London.
[14] Food and Agriculture Organization of the United Nations, World Organization for Animal Health and World Health Organization (2020). Technical Brief on Water, Sanitation, Hygiene and Wastewater Management to Prevent Infections and Reduce the Spread of Antimicrobial Resistance. Geneva.
[15] United Nations Environment Programme (2023). Bracing for Superbugs: Strengthening environmental action in the One Health response to antimicrobial resistance. Geneva.
[16] The Access to Medicine Foundation (2023). Methods matter: What steps are companies taking to help curb AMR by manufacturing responsibly?. Amsterdam.

comprehensive risk management. It also emphases the need to incentivise procurement processes. When considering the inclusion of this guidance in regulatory and legally binding processes, risks to access and price should be carefully considered. A reasonable implementation time should also be recommended to balance potential risks to access with the risks to resistance development and ecological effects in the absence of an adequate management of the emissions . In situations where adherence to the guideline criteria is discretionary, and the financial burden primary falls on the purchasing party (such as award-criteria during procurement or subsidy-decisions), the risks for access problems or price hikes should be minimal. In such cases, the purchasing side is encouraged to offer incentives that vary based on the level of pollution control demonstrated by the seller.

How was the guidance developed?

This guidance was developed under the supervision of the WHO steering group with a multidisciplinary group of experts with expertise in AMR, waste and effluent management, pharmaceutical manufacturing practices that was screened for conflicts of interest.

Multiple lines of evidence were used to inform the guidance development including scientific evidence synthesis for PNECs for resistance selection, a review of waste and wastewater technologies used in antibiotic manufacturing and grey literature review for implementation of similar guidance from industry and national and regional efforts .

Expert opinion from a larger group of external WHO experts accounting for diverse areas of expertise related to the guidance, geographical and gender balance was also sought thought all the development of the document Experts were screened for conflicts of interest.

An initial draft was developed by the WHO steering and expert group. This was made available for public consultation for period of six weeks from December 2023 to 9February 2024. Feedback was received from 23 individuals and/or organisations. Feedback was collated and discussed with the steering and expert groups. All feedback from the public consultation was synthesised and responded to and updates made to the guidance as necessary. Decisions were made on the written and verbal feedback based on the following criteria: feasibility for immediate or stages implementation, intervention/option(s) acceptable to all stakeholders, balance between benefits and harms, impact on equity.

A public hearing was also organized from those who had submitted specific feedback on 2 May 2024 to provide stakeholders the chance to present their view. A final draft was shared with the WHO steering and expert group for final review and feedback incorporated to generate the final guidance document.

Is this guidance binding?

This guidance is not legally binding. Application of this guidance might result in its targets and risks management process being integrated into binding texts related to antibiotic manufacturing and procurement.

The purpose of this document is to offer independent, scientifically robust targets and risks management guidance so that the primary audiences can reference and utilise contents of the guidance within their respective roles related to pharmaceutical manufacturing. For example, auditors may integrate the guidance, whole or in part, procurers may design incentive schemes to improve manufacturing processes through their procurement, regulation may integrate aspects of the guidance to drive improvements in manufacturing processes over time.

What are next steps to implementing the guidance?

The document will be shared among key audiences that will be informed and sensitized also through specific meetings and webinars. It will be also promoted at relevant conferences and events. The key audience will be targeted by specific initiatives according to their role/function within the health and pharmaceutical manufacturing systems.

WHO will monitor the uptake and implementation of this document by the target audiences. Who will also monitor new scientific literature on this topic to assess its implementation or detect specific gaps and needs. Learning from implementation, and new research, will inform future updates of this guidance, including possible future inclusion of aspects out of scope such as other antimicrobials. It is also envisaged that PNEC target data will be periodically reviewed as new data emerges and technologies for detection of PNEC targets are improved or made available.