ENVIRONMENTAL ASPECTS OF MANUFACTURING FOR THE PREVENTION OF ANTIMICROBIAL RESISTANCE

Antimicrobial resistance (AMR) is a global and multisectoral challenge that requires a comprehensive One Health response to bridge human, animal, plant and environmental health. The environment is considered as one driver/reservoir of AMR as the discharge of antimicrobial residues and resistant microbes from health care facilities, household and farms and pharmaceutical manufacturing can potentially increase the risk of AMR infections.\(^1\)

According to research by UN Environment,\(^2\) 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. There is an emerging evidence showing that pharmaceutical plants can act as hotspots that release large amounts of antibiotics into the environment, which is of particular concern in the regions without adequate monitoring and wastewater management capacity.

The Organisation for Economic Cooperation and Development (OECD) in its latest report “Pharmaceutical Residues in Freshwater” (November 2019), highlights the need to better understand the effects of pharmaceutical residues in the environment, and to employ policy instruments across the pharmaceutical life-cycle to mitigate the risks, by improvements in the design, authorization, production, use, solid waste and wastewater treatment. A focus on preventive options early in the pharmaceutical life-cycle, including production, may deliver the most long-term, cost-effective and large-scale benefits\(^3\).

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Against a backdrop of rising global concern about AMR, following up on the Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) request from October 2018, the WHO Secretariat developed a document outlining points for manufacturers and inspectors to consider in preventing AMR. This Points to Consider document addresses also the November 2018 decision of the World Health Organization (WHO) Executive Board to provide technical input to good manufacturing practices guidance on waste and wastewater management from the production of critically important antimicrobials for human medicine.

The ECSPP at its last meeting in October 2019 adopted the text “Environmental aspects of manufacturing for the prevention of antimicrobial resistance” that is going to be published in spring 2020 as an Annex to the ECSPP report in the WHO Technical Report Series (TRS).

The purpose of the document is to leverage on the current WHO Good Manufacturing Practices (GMP) with the following objectives:

- raise awareness among manufacturers, GMP inspectors and inspectorates of the existing GMP guidance that applies to the production of antimicrobials;
- encourage Member States to establish and enforce appropriate requirements on their local pharmaceutical production facilities; and
- consider options for reducing and mitigating the uncontrolled disposal of waste and wastewater containing antimicrobials, with a focus on the role of GMP and inspectors in this.

The first draft of the document (April 2019) prepared by WHO Prequalification (PQ) Team - Inspections and the WHO Secretariat was reviewed by WHO colleagues from the AMR Surveillance, Prevention and Control Department within the AMR Division, and then it was mailed to the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations inviting their comments. The document was also posted on the WHO website for public consultation (May-June 2019). In addition, it was discussed during several international meetings. All the comments received were consolidated and discussed during the Informal Consultation on Good Practices for Health Products Manufacture and Inspection (Geneva, July 2019).

During the GMP consultation on Good Practices for Health Products Manufacture and Inspection (Geneva, July 2019), some proposals were discussed including:

a. the potential role of GMP inspectors to tackle AMR; and
b. the need to revise the WHO GMP main text in order to specifically address this issue.
The main limitations identified when considering broadening up either the current WHO GMP scope or the role of the inspectors to encompass environmental aspects were the following:

i. GMP inspectors may not be adequately trained for inspecting waste and wastewater management processes on a required level and that the duration of GMP inspections, being limited to no more than 2 to 5 days, depending on the type of site, should not be considerably extended to cover those aspects.

ii. The competence on environmental issues is often with environmental inspectors reporting to a different authority with specific competences and mandate.

iii. There are no WHO or government-developed thresholds (only industry ones) on the acceptable residual limits from antimicrobial production in waste and wastewater to perform a meaning evaluation.

iv. The knowledge on the waste and wastewater treatment is limited for most GMP inspectors, therefore additional training in this area may be required if they are to verify those aspects.

v. This Point to consider document focuses purely on the contamination of the environment through production and does not attempt to address the many other drivers of AMR and the life-cycle of managing medicines in the environment.

vi. The potential challenges to implementing the points to consider in practice and the importance of ensuring collaboration between product and environment inspections were also acknowledged.

After a careful reflection of the pros/cons and the stated limitations, the document was restructured and the main changes were made to narrow the scope and structure of the initial document by:

- including the relevant text from the GMP guidelines\(^4\) relating to environment protection and waste management to prevent AMR in the main body;
- elaborating on recommendations to manufacturers, including explanations on the clauses listed to clarify the expectation of Inspectors from manufacturers in this area;
- focusing on the new target audience, namely pharmaceutical manufacturers and GMP inspectors; and
- amending the scope: it is now drafted as a policy document for use by manufacturers when designing and selecting their waste management processes, when performing self-audits and also for use by both inspectors and manufacturers during GMP inspections of pharmaceutical manufacturing sites.

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\(^4\) WHO Good Manufacturing Practices for Pharmaceutical Products containing Hazardous Substances (WHO TRS No. 957, 2010, Annex 3)
The *Point to Consider* document discussed and adopted by the 54th ECSPP last October 2019 will be used in conjunction with a survey of waste and wastewater management practices that will be sent to manufacturers to raise awareness of AMR and to verify the practices currently in use in the industry as well as the application of the recommendations made in the newly-adopted *Points to Consider for manufacturers and inspectors: Environmental aspects of manufacturing for the prevention of antimicrobial resistance.*

The WHO Prequalification (PQ) Team – Inspections is also initiating a phased approach in the verification of the waste and wastewater management practices in use at pharmaceutical manufacturing sites who are active in the production of antimicrobials during onsite inspections in 2020.

Results of the survey will be presented to the 55th ECSPP in 2020.

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