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ENVIRONMENTAL ASPECTS OF GOOD MANUFACTURING PRACTICES: POINTS TO CONSIDER FOR MANUFACTURERS AND INSPECTORS IN THE PREVENTION OF ANTIMICROBIAL RESISTANCE

(May 2019)

DRAFT FOR COMMENTS

Please send any comments you may have to Dr Valeria Gigante (gigantev@who.int), Technical Officer, Medicines Quality Assurance, with a copy to Claire Vogel (vogelc@who.int) by 14 June 2019.

Medicines Quality Assurance working documents will be sent out electronically only. They will also be placed on the Medicines website for comment under "Current projects". If you have not already received our draft working documents, please send your email address (to jonessi@who.int) and we will add you to our electronic mailing list.

SCHEDULE FOR DRAFT WORKING DOCUMENT QAS/19-802:

ENVIRONMENTAL ASPECTS OF GOOD MANUFACTURING PRACTICES: POINTS TO CONSIDER FOR MANUFACTURERS AND INSPECTORS IN THE PREVENTION OF ANTIMICROBIAL RESISTANCE

Description of Activity	**Date**
During the Fifty-third World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP), the Expert Committee recommended to develop a document as "points to consider" on environmental aspects relating to manufacturing for the prevention of antimicrobial resistance (AMR), to possibly include the role of inspectors.	22-26 October 2018
Preparation of the first draft working document by Ms Stephanie Croft from the WHO Prequalification (PQ)-Team Inspection.	February 2018 - March 2019
Circulation of the draft document to WHO colleagues working in the area of AMR and to WHO (PQ)-Team Inspection and inclusion of their feed-back in the draft document.	April 2019
Mailing of working document to the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations (EAP) inviting comments and posting of the working document on the WHO website for public consultation.	May – June 2019
Discussion of working document during the Joint Meeting on Regulatory Guidance for Multisource Products.	Copenhagen, 17-18 May 2019
Consolidation of comments received and review of feedbacks. Preparation of working document for discussion.	June 2019

Discussion of working document and feedbacks received during the informal Consultation on Good Practices for Health Products Manufacture and Inspection.	July 2019
Revision of the working document based on comments received during the informal Consultation on Good Practices for Health Products Manufacture and Inspection.	End of July 2019
Mailing of revised working document to the EAP inviting comments and posting the working document on the WHO website for public consultation.	August – September 2019
Consolidation of comments received and review of feedbacks. Preparation of working document for discussion.	End of September 2019
Presentation to the Fifty-fourth meeting of the ECSPP.	14 -18 October 2019
Any other follow-up action as required.	

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ENVIRONMENTAL ASPECTS OF GOOD MANUFACTURING PRACTICES: POINTS TO CONSIDER FOR MANUFACTURERS AND INSPECTORS IN THE PREVENTION OF ANTIMICROBIAL RESISTANCE

1. INTRODUCTION AND SCOPE

1.1. Background

Growing antimicrobial resistance (AMR) linked to the discharge of drugs and particular chemicals into the environment is one of the most worrying health threats today, according to research by UN Environment (*1*). AMR accounts for an estimated 700 000 deaths per year 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 resolutions on AMR. This 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) Executive Board meeting decided that technical input will be provided to Good Manufacturing Practice (GMP) guidance on waste and wastewater management from the production of Critically Important Antimicrobials (*5*, *6*). This "points to consider" document was written further to this recent decision.

This document is to be considered as a time-limited document that addresses the current needs for guidance on how GMPs should be implemented to waste and wastewater management for production of antimicrobials, with a focus on Critically Important Antimicrobials. Wherever possible, this text is informed by relevant evidence. However, the evidence base may be weak in some areas, therefore inputs from stakeholders and experts could be beneficial.

1.2. Purpose

The purpose of this document is to:

- Raise awareness of medicines' manufacturers, GMP inspectors and inspectorates in all Member States on sections of relevant GMP guidance that are applicable to the management of waste/wastewater from the production of antimicrobials.

- 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.

- Raise awareness of medicine's manufacturers, GMP inspectors and inspectorates, on the importance of considering all aspects of GMP implementation and to also focus on the parts of GMP that may not have a direct product quality impact.

- Raise awareness of Member States, to establish and enforce requirements for their local pharmaceutical production facilities to safely dispose of the waste and wastewater that is generated while manufacturing antimicrobials, with a focus on Critically Important Antimicrobials.

- Provide proposals on what should be done by the different stakeholders in order to help control and reduce contamination of the environment with antimicrobials and related chemicals coming from pharmaceutical production processes.

- Discuss options and tools to reduce and mitigate the uncontrolled disposal of waste and wastewater containing antimicrobials when manufacturing medical products, with a focus on how GMP can more comprehensively address environmental aspects in the prevention of AMR, including the potential role of inspectors to tackle this issue. This includes:

    - a presentation of a pilot process in the WHO Prequalification (PQT) Inspectorate to comprise verification of adequate preventive measures in place to prevent environmental contamination with Critically Important Antimicrobials manufactured at medicines manufacturing facilities, involving both active pharmaceutical ingredient (API) and finished pharmaceutical product (FPP) production facilities;

    - a discussion of a proposal to update GMP guidelines, with a focus on the guidelines *WHO good manufacturing practices for pharmaceutical products containing hazardous substances* (*Annex 3, TRS957, 2010)* (*7*)*;*

    - a discussion of the creation of a network/forum coordinated by WHO to share information, experience and mechanisms for reporting eventual potential breaches of national/international laws on waste discharge; and

    - a proposal to initiate an awareness campaign among Member States, which includes GMP inspectors.

- Gather stakeholders' inputs on potential way forwards to tackle AMR, including successful experiences and best practices when manufacturing pharmaceutical products.

This document is not intended to cover AMR issues that are related to the clinical or veterinary setting or to other types of environmental contamination (*1*) (such as the excretion of antimicrobials during their use).

1.3. Target audience

This document is primarily targeted to:

- All manufacturers of antimicrobials who are involved in the manufacturing of API and FPPs.

- GMP inspectors and inspectorates from national medicines regulatory authorities.

- Regulatory bodies that are responsible for enforcing environmental protection standards and waste/waste water management in all Member States; consistent with a multidisciplinary approach, the Ministries of Health, Ministries of Environment or Pollution control boards and Ministries of Agriculture, as appropriate.

- Waste and wastewater management services who handle antimicrobial waste and/or process effluents from the pharmaceutical industry.

- Procurement agencies who are purchasing antimicrobials and, more particularly, Critically Important Antimicrobials, who include a verification of compliance with GMP requirements as part of their quality assurance process and/or who aim to purchase antimicrobial medicines from companies who have sustainable and environmentally respectful production processes.

- NGOs and other non-state actors who are involved in monitoring and mitigating AMR.

- Experts in environmental development and the spread of AMR, with a focus on the release of antimicrobials from manufacturing.

- Experts in waste and wastewater treatment technologies applicable in antimicrobial manufacturing.

2. GLOSSARY

The definitions given below apply to the terms as used in these guidelines. They may have different meanings in other contexts.

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.

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.

Finished pharmaceutical product (FPP)

A finished dosage form of a pharmaceutical product, which has undergone all stages of manufacture, including packaging in its final container and labelling.

3. IMPACT OF API AND FPP PRODUCTION PROCESSES ON ANTIMICROBIAL-RESISTANCE

We may be 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 (*1*).

The environment is key to antibiotic resistance. Bacteria in soil, rivers and seawater can develop resistance through contact with resistant bacteria (transfer of resistance genes), antibiotics, 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*).

The levels of pollution with antibiotics 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 hot spots for antimicrobial resistance development, but this knowledge dates from only a few years ago (*11*).

Poor control of waste and wastewater, such as that encountered in some of the countries who are major global producers of APIs and FPPs, can often lead to the entry of antibiotics into waters that are contaminated with pathogenic bacteria from untreated sewage. This increases the risk of the development of antimicrobial resistance. Furthermore, a vast array of contaminants in municipal and industrial wastewater increases pressure on bacteria to become resistant (*1*, *11*).

Concentrations in river water depend on wastewater treatment facilities as well as antibiotic 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*). Often, there is little or no treatment of manufacturing effluents or pharmaceutical waste leaving municipal wastewater treatment plants to handle the waste. However, the activated sludge 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 before disposal into the environment.

Action has already been initiated by some Member States, however, most of the Critically Important Antimicrobials are being manufactured in countries where legislation on environmental protection is still in its infancy and its enforcement is considered to be a challenge.

Example box

In the European Union (EU), there are legislative measures in place to control industrial pollution and to prevent the contamination of the water environment by listed priority substances (*13*). However, new measures are soon to be proposed through the new One Health action plan (14) to specifically focus on limiting antimicrobial discharges from the pharmaceutical manufacturing process in the EU.

There is an urgent call for cross-cutting pluri-sectorial action with a strong coordination and action plan coming from Ministers of Health.

Manufacturers of antimicrobials, with a special focus on API manufacturers, should implement waste stream analyses, waste management and wastewater treatment at source. Some manufacturers have launched voluntary initiatives in this regard. In 2016, a number of pharmaceutical companies presented a roadmap on combating AMR in the run-up to the United Nations General Assembly (UNGA) High-level Meeting on AMR. It committed to a list of actions, including taking action on their own manufacturing and supply chains for managing antibiotic discharge and the establishment of science-based, risk-driven targets in order to establish good practices reducing the environmental impact of manufacturing discharge by 2020 (*15*).

The contributions of GMP inspectors/inspectorates, procurers, NGO's/Non-state actors are also of particular importance.

4. REVIEW OF ENVIRONMENTAL ASPECTS OF GMP

GMP are, a priori, intended to control the manufacture of the 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 waste of all sorts appearing in 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. No major new class of antibiotics have been discovered since 1987 and too few antibacterial agents are in development to meet the challenge of multidrug resistance (*16*).

The WHO GMP main principles for pharmaceutical products text (*17*) and WHO GMP for APIs (*18*) contain a limited set of clauses related to environmental issues. Waste and wastewater management is addressed only briefly.

On the other hand, the *WHO good manufacturing practices for pharmaceutical products containing hazardous substances* (*Annex 3, TRS957, 2010)* (*7*) contains more detailed requirements regarding waste and wastewater management which can be applied to the production of antimicrobials (see Appendix 1 for relevant clauses). These guidelines cover those hazardous substances traditionally belonging to reproductive health hormones and highly potent or sensitizing medicines such as steroids, cephalosporins and 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, when released into the environment through their action on microorganisms, are deemed to present a substantial risk of injury to both health and the environment, they should be considered for inclusion in the scope of this guidance.

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

The guidance currently requires that the external atmosphere and the public near the facility should be protected from harm from hazardous substances.

The guidance already requires neither the product or its residues of hazardous products handled in a facility should be allowed to be discharged directly to normal drainage systems.

The guidance states that if liquid effluent poses a safety or contamination risk, the effluent should be treated before being discharged to a municipal drain. However, manufacturers seem not to have noted this, 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.

The guidance also contains the general statement that liquid and solid waste effluent should be handled in such a manner as not to present a risk of contamination to the personnel or to the environment.

It also states that all effluents should be disposed in a safe manner and that 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.

The guidance currently requires that the external atmosphere and the public near the facility should be protected from harm from hazardous substances.

The documents that the manufacturing facilities should possess are not explicit in this guidance. Manufacturers, however, would be expected to retain documentation on the following:

- Waste stream analysis for each antimicrobial agent produced, updated whenever there is a change in production affecting waste streams.

- The quantity and nature of the waste generated, including documentation of analysis performed and their findings on the hazardous substances it contains.

- Monthly reports on its collection, treatment and disposal.

- Information on the methods used to treat the waste – they should be documented to be effective for each specific hazardous substance contaminant. Analytical data demonstrating the conversion of hazardous 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 concerning each API or FPP, documentation on a time-limited strategy should be in place with specified milestones for that implementation.

This documentation should be maintained at the facility regardless of whether or not an external contractor has been used.

5. PROPOSALS FOR STAKEHOLDERS

5.1. Manufacturers of medicines

FPP and API manufacturers should thoroughly examine their waste and waste management processes to ensure that antimicrobial residues are treated in a safe and effective manner. The industry could take a role in developing standards for pharmaceutical waste containing antimicrobials.

5.2. National GMP inspectorates from all Member States

The following actions are proposed:

- Implementation of WHO guidelines on hazardous substances or equivalent GMP guidelines to the production of antimicrobials.

- Train inspectors on inspection of waste and wastewater management processes and instruct inspectors to include inspection of those aspects for all sites who are manufacturing Critically Important Antimicrobials during routine GMP inspections.

- Increase the level of communication between the GMP inspectorates and their local national regulatory bodies who are responsible for enforcing environmental protection standards.

5.3. Regulatory bodies responsible for enforcing environmental protection from pharmaceutical waste

In all Member States, consideration should be given to developing national action plans for AMR and for strengthening the legislation for waste and wastewater management and its enforcement.

Inspectors within the relevant departments (e.g. Ministries of Health, Ministries of Environment or Pollution Control Boards) of waste/wastewater treatment plants should be trained on aspects relating to decontamination of antimicrobials.

Programs for sampling and testing of wastewater and effluents should be implemented to monitor compliance with local/international regulation and with the effectiveness of the decontamination and mitigation strategies.

5.4. Procurers of antimicrobial medicines

Procurement agencies who purchase antimicrobials, particularly Critically Important Antimicrobials, are encouraged to purchase those medicines from companies who have sustainable and environmentally respectful production processes.

6. PROPOSAL FOR WHO'S OPTIONS AND TOOLS USING WHO GMP

While focusing on how WHO can more comprehensively address environmental aspects for the prevention of AMR and the potential contributing role of inspectors to tackling this issue, WHO has the following options and tools to reduce and mitigate the uncontrolled disposal of waste and wastewater containing antimicrobials when manufacturing medical products.

6.1 Pilot process in the WHO PQT Inspectorate

A pilot process will be initiated by 2020 by WHO's Prequalification Team Inspectorate (*19*) to include verification of adequate measures to prevent environmental contamination with antimicrobials. It will focus on Critically Important Antimicrobials manufactured at both APIs and FPPs' medicines manufacturing facilities. The *WHO good manufacturing practices for pharmaceutical products containing hazardous substances* (*Annex 3, TRS957, 2010)* will continue to be enforced during inspections with an increased level of scrutiny for Critically Important Antimicrobials. Deficiencies should be noted in case of non-compliances.

Adequate corrective and preventive actions will be verified for those deficiencies and will be a condition for making a conclusion on the level of GMP compliance of manufacturing sites.

After each successful facility inspection close-out, a WHO Public Inspection Report is published (*20*). To provide greater transparency and to enable the verification of adequate compliance with requirements by stakeholders, consideration should be given to including a section in the WHO Public Inspection Reports on waste and wastewater management. This would provide a means for procurers to make informed decisions, taking into consideration the environmental impact of the medicines they purchase.

Approximately one year after its launch, the effectiveness of this pilot process will be monitored to decide whether or not it should be modified, strengthened or expanded.

6.2 Proposal to update GMP guidelines

The following modifications to the guidelines *WHO good manufacturing practices for pharmaceutical products containing hazardous substances* (*Annex 3, TRS957, 2010)* should be considered:

- To enable a thorough and effective verification of compliance and to avoid the use of external contractors as a loophole, manufacturing facilities should be specifically required to possess adequate documentation. This should include:
    - documentation of waste stream analysis for each API or FPP;
    - the quantity and nature of the waste generated, including analytical information on the hazardous substances it contains;
    - monthly reports on its collection, treatment and disposal;
    - for facilities with already implemented waste treatment, information on the methods used to treat the waste – they should be documented to be effective for

each specific hazardous substance contaminant. Analytical data demonstrating the conversion of hazardous substances and their residues to non-hazardous waste materials should be available at the facility and kept up to date; and

- for facilities without waste treatment of all waste streams, a time limited strategy should be in place, specifying actions towards achieving treatment that significantly reduces the concentration of the API (and its microbial source, when relevant) or FPP.

This documentation should be maintained at the facility regardless of whether or not the facility treats its own waste or discharges it to an external contractor or third party waste water treatment plant, with or without pretreatment (e.g. pH adjustment, chelation, precipitation, etc.).

- The guidance currently requires that the external atmosphere and the public in the vicinity of the facility should be protected from harm from hazardous substances. In the proposed revision, the inclusion of effluents and water streams should be considered in this section because the literature contains several reports of effluents close to facilities being contaminated with dangerous levels of antimicrobials.

- Including guidance on acceptable methods of decontamination of manufacturing waste containing antimicrobials and on mitigation strategies. Many decontamination methods already exist that reduce or remove antibiotics (and microbes that have produced fermentative antimicrobials) from waste streams entering the environment from antimicrobial manufacturing: secondary and tertiary waste water treatment; membrane filtration and ozonation; and UV 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 level of effectiveness and by-products should be considered when adopting a particular approach.

6.3 Creation of a network/forum coordinated by WHO

Currently, there are no established mechanisms to share information, know-how, mechanisms or instruments to report an eventual breach of national/international laws on waste discharge. Establishing a multi-disciplinary network of experts and regulators would be key to improving the sharing of information between inspectorates and the relevant departments of Member States so that appropriate action is taken in a timely manner in the event of any breaches. Procedures should be established for communication between WHO, GMP inspectorates and all relevant regulators from Member States, independent technical experts and research groups on AMR.

6.4 Awareness campaign among Member States

WHO has launched awareness campaigns on antimicrobial resistance in several regions. However, there have not yet been any campaigns specifically targeted at the production of antimicrobials and towards waste and wastewater management. This should be considered for inclusion in future campaigns. GMP inspectorates, regulatory bodies that are responsible for enforcing environmental protection standards and waste/wastewater management such as Ministries of Health, Ministries of Environment or Pollution Control Boards and Ministries of Agriculture should also be targeted by those campaigns.

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ACRONYMS

AMR: Antimicrobial resistance
API: Active pharmaceutical ingredient
ARB: Antibiotic resistant bacteria
ARG: Antimicrobial resistance gene
FPP: Finished pharmaceutical product
GMP: Good manufacturing practices
UNGA: United Nations General Assembly

Appendix 1

Relevant sections of WHO guidelines and proposals for modification

A. ANNEX 3, TRS 957, 2010. GUIDANCE ON WHO GOOD MANUFACTURING PRACTICES FOR PHARMACEUTICAL PRODUCTS CONTAINING HAZARDOUS SUBSTANCES

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.

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.

7. **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.

7.2 The external atmosphere and the public in the vicinity of the facility should be protected from possible harm from hazardous substances.
(Note from Secretariat: effluents or water streams should also be considered.)

7.3 If liquid effluent poses a safety or contamination risk, the effluent should be treated before being discharged to a municipal drain.
(Note from Secretariat: the municipal drain may not be suitable to handle large quantities of hazardous effluents and therefore manufacturers are requested to consider this in their approach.)

13. **Effluent treatment**

13.1 Liquid and solid waste effluent should be handled in such a manner so 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.
(Note from Secretariat: manufacturers should possess adequate and detailed documentation on those aspects.)

B. ANNEX 2, TRS957, 2010. WHO GOOD MANUFACTURING PRACTICES FOR ACTIVE PHARMACEUTICAL INGREDIENTS

4.6 **Sewage and refuse**

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.

C. ANNEX 2, TRS986, 2014. WHO GOOD MANUFACTURING PRACTICES FOR PHARMACEUTICAL PRODUCTS: MAIN PRINCIPLES

14.4 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.