World Health Organization

African Region

Technical guidance and aide-mémoire

on good manufacturing practice inspection of pharmaceutical manufacturing facilities with focus on reducing the incidence of antimicrobial resistance

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Effluent treatment plant

Piloting the inspection tools in Zambia

Piloting the inspection tools in Uganda

World Health Organization
African Region

Technical guidance and aide-mémoire on good manufacturing practice inspection of pharmaceutical manufacturing facilities with focus on reducing the incidence of antimicrobial resistance

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Contents

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Glossary

The definitions given below apply to the terms used in this guide. They may have different meanings in other contexts.

Antimicrobial

Antibiotics, antivirals, antiparasitics and antifungals.

Antimicrobial resistance

The development of resistance in a microorganism (bacterium, virus, fungus, or parasite) to an antimicrobial agent to which it was previously sensitive. The development of resistance while a natural evolutionary process is linked to increased selection pressure as a result of misuse and abuse of antimicrobials. 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 antimicrobial treatment for 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, surface waters 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. (1)

Effluent

Waste water or other fluid of domestic agricultural trade or industrial origin, treated or untreated and discharged directly or indirectly into the aquatic environment.

Environment

The physical factors of the surroundings of human beings, including land, water, atmosphere, climate, sound, odour, taste, the biological factors of animals and plants and the social factor of aesthetics and includes both the natural and the built environment.

Inspector

Refers to a competent person from a national regulatory authority or from a manufacturer of medical products, who conducts good manufacturing practice inspection.

Minimum inhibitory concentration (MIC)

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

One Health

One Health is an approach to addressing antimicrobial resistance (AMR) that recognizes the interconnections between human, animal, and environmental health. It emphasizes the need for collaboration across sectors and disciplines to effectively address AMR. (3)

Pollution

Any direct or indirect alteration of the physical, thermal, chemical, biological or radioactive properties of any part of the environment by discharging, emitting or depositing wastes so as to affect any beneficial use adversely, to cause a condition which is hazardous or potentially hazardous to public health, safety or welfare, or to animals, birds, wildlife, fish or aquatic life, or to plants.

PEC (Predicted environmental concentration)

The calculated concentration of a chemical in the environment. This is based on modeling and third-party data derived from known environmental persistence (ability to be degraded), transport (ability to penetrate biological membranes and accumulate inside flora and fauna), and fate (the ability for organisms in the environment to metabolize and detoxify the pharmaceutical, nullifying any detrimental effects arising from the bioaccumulation of the pharmaceutical).

PNEC

The concentration of a chemical which marks the limit at which below no adverse effects of exposure in an ecosystem are measured. Predicted No-Effect Concentration (PNEC) values are intended to be conservative and predict the concentration at which a chemical will likely have no toxic effect. They are not intended to predict the upper limit of concentration of a chemical that has a toxic effect. PNEC values are often used in environmental risk assessment as a tool in ecotoxicology. (4)

PNEC-Environment (PNEC-ENV)

Values based on eco-toxicology data and are intended to be protective of ecological species and incorporate assessment factors consistent with standard environmental risk methodologies.

PNEC-Minimum Inhibitory Concentration (PNEC-MIC)

The values are based on the approach published in (5) and are intended to be protective of resistance promotion.

Abbreviations

AHU	Air handling unit
ALCOA	Attributable, legible, contemporaneous, original, accurate
AMR	Antimicrobial resistance
API	Active pharmaceutical ingredient
CIP	Clean-in-place
COP	Clean-out-of-place
ENV	Environment
FPP	Finished pharmaceutical product
GMP	Good manufacturing practice
HEPA FILTER	High efficiency particulate air filter
HVAC	Heating, ventilation and air-conditioning
MAL	Material airlock
MIC	Minimum inhibitory concentration
PAL	Personnel airlock
PEC	Predicted environmental concentration
PNEC	Predicted no-effect concentration
SOPs	Standard operating procedures
TRS	Technical report series
WHO	World Health Organization
WIP	Work-in-progress

1.0

Introduction

1.1

Background to antimicrobial resistance

1.1.1 Global threat of antimicrobial resistance

Antimicrobial resistance (AMR) has been a health policy challenge for the past 75 years, although response has varied greatly over time, and between countries and regions. Every year at least 700,000 people die from drug-resistant infections. If AMR remains unchecked, the annual death toll could rise to 10 million people by 2050. (6)

At the Sixty-eighth World Health Assembly in May 2015, Member States endorsed the Global Action Plan on Antimicrobial Resistance which espouses the one health approach to tackle antimicrobial resistance the most urgent threat to modern medicine.

The action plan includes a framework which calls for antibiotic-specific regulatory approaches and controls to curb AMR incidence and ensure safe and rational use of antibiotics. This underscores the need for regulators of medical products to play a key role in prevention and detection of AMR.

1.1.2 Factors leading to development of resistance

The common factors leading to AMR include:

(a) patient use of antibiotics for viral infections or other ailments not caused by bacteria and use of incorrect dosages, which exposes bacteria needlessly to antibiotics. This exposure presents the selective pressure necessary to allow antibiotic resistant bacteria to emerge;

(b) antibiotic use in animals as a protective measure or to promote growth, which increases human antibiotic exposure through the food chain, and the environment from animal waste;

(c) manufacturing effluents from antibiotic production sites that are discharged into the environment, also contribute to AMR development;

(d) the elevated presence of antibiotics in the environment which is believed to be increasing the rate of antibiotic resistance selection; and

(e) use of medicines adulterated with antimicrobial products, due to cross-contamination. This can lead to exposure of bacteria (in humans, animals and the environment) to sub-therapeutic levels of an antimicrobial product that are several hundred-fold below the Minimum Inhibitory Concentration (MIC) and promote development of resistant bacterial strains.

1.1.3 Reducing the incidence of AMR

One of the interventions for reducing the incidence of AMR involves reducing the environmental impact from the production of antibiotics. Particularly, the use of appropriate measures based on risk to adequately control manufacturing effluent emissions into the environment.

1.1.4 Tackling the AMR problem

Tackling the challenge of antimicrobial resistance requires a One Health perspective that considers human health, animal health, and the environmental dimension of AMR. In line with the World Health Organization. (2015). Global action plan on antimicrobial Resistance, it is crucial that all stakeholders be involved in effective stewardship across antibiotic production, use and disposal. (6i)

1.2 Overview of the technical guidance and aide-mémoire

This Technical Guidance and Aide-Mémoire focuses on waste management and cross-contamination issues that inspectors need to consider during their routine inspections of manufacturing sites for antimicrobial products as part of the campaign for effective antimicrobial stewardship. It is expected that elements of the Aide-Mémoire will form part of most Good Manufacturing Practice (GMP) inspections whereby inspectors will be reminded of the specific areas to focus on and identify triggers for any inappropriate practices of a manufacturer that can contribute to the risk of antimicrobial resistance. Hence, this document should serve as a guidance document only and is not exhaustive or prescriptive, and does not imply that specific inspections of waste management and cross-contamination control systems be performed.

1.3 Objective of this technical guidance and aide-mémoire

The aim of this document is to provide the key areas relating to waste management and protection of the environment from antimicrobial waste, and prevention of cross-contamination that inspectors need to consider in embedding the AMR perspective into their routine regulatory GMP inspection practices, or self-inspection and/or internal audit procedures for manufacturers of medical products.

1.4 Scope of this technical guidance and aide-mémoire

This document applies to all areas and situations where the handling of antimicrobial substances, ingredients or products could lead to cross-contamination, exposure of personnel, or discharge to the environment. This includes manufacturing sites for antimicrobial ingredients and finished products for human and veterinary use.

This document may also apply to out-sourced institutions/companies that handle or dispose of hazardous waste containing antimicrobial waste e.g. those that launder protective clothing contaminated with antimicrobial powder/dust and those that transport, store or dispose of antimicrobial waste.

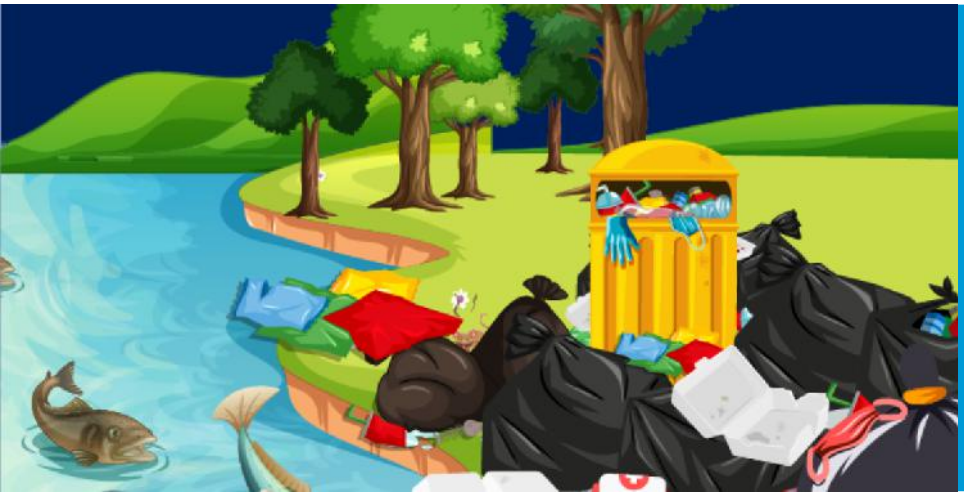
1.5 How to use this technical guidance and aide-mémoire

This document should be read in conjunction with other WHO Good Manufacturing Practice guidelines that are referenced in the Aide-Mémoire under the column "Reference".

The Aide-Mémoire has high level questions that the inspector needs to take into account in the search for objective evidence. This means that the inspector has to formulate lower level questions as may be required, use appropriate questioning techniques and examine (and/or observe) documents (including records), materials, processes, work-in-progress, equipment, premises, environment, people, etc., and verify that the defined system elements exist, are adequately implemented, are effective, and are well maintained.

2.0

Technical guidance



2.1

Waste management

2.1.1 GMP/ Environmental Protection Requirements

"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.

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". (7)

"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". (8).

2.1.2 Interpretation of requirements

Manufacturers of antimicrobial agents should develop robust antimicrobial-containing waste management processes that ensure that the amount of antimicrobial agents discharged into the environment from factory waste is controlled and monitored.

It is expected that manufacturing facilities for antimicrobial agents should have properly designed effluent treatment plants and/or systems. The effluent treatment plants and equipment should be well maintained.

Manufacturers are expected to demonstrate that the amount of antimicrobial agents in the various forms of waste from the factory is quantifiable, monitored and controlled before discharge into the environment through various channels.

Waste water should be tested to quantify the amount of antimicrobial agents discharged into the municipal sewerage system or other environmental water collecting bodies.

2.1.3 Implications for inspector

The inspector should refer to the requirements in section 2.1.1 above and to the items in section 1.0 of the Aide-Mémoire and verify, among other things, that antimicrobial agents are adequately decontaminated before being discharged into the municipal sewerage system or the environment.

The inspector should verify the schematic drawings of the effluent treatment plant, and check for the process flow from factory to effluent treatment plant to the point of entry into the municipal sewerage system or the environment.

2.2 Antimicrobial resistance site risk assessment

2.2.1 GMP/ Environmental Protection Requirements

"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 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 and/or 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." (9).

2.2.2 Interpretation of requirements

Manufacturers should perform site risk assessment(s) to determine the likelihood of their processes to lead to the development of AMR.

The amount of antimicrobial agents discharged into the environment should be below concentrations that have potential to give rise to the development of antimicrobial resistance.

Manufacturers should quantify the amount of antimicrobial agents they discharge into the environment. This is called the Predicted Environmental Concentration (PEC) for each antimicrobial agent.

For each antimicrobial agent, the manufacturer should determine the minimum concentration required to cause the development of resistant microbes. This is called the Predicted-No-Effect Concentration (PNEC) value. One of the sources for the PNEC values is the AMR Industry Alliance (10).

2.2.3 Implications for inspector

The inspector should refer to the requirements in section 2.2.1 above and to the items in section 2.0 of the Aide-Mémoire and verify, among other things, how the site has quantified the amount of antimicrobial agent discharged into the environment (PEC value). This allows manufacturer to calculate their eco-toxicological risk quotient and propose ways to mitigate the risk.

The inspector should request for the list of products manufactured at the site and identify all the antimicrobial agents. For each antimicrobial material or product on the list, the inspector should request for documentation for the PNEC value being used and how or where it is derived from.

PNEC values, based on the minimum inhibitory concentration (MIC) of the antibiotic, are intended to guide environmental regulation and monitoring programmes in efforts to keep environmental antibiotic concentrations below a certain level that will not likely promote AMR development and spread.

The inspector should review the calculation of the site risk assessment to the development of resistant microorganisms using the ratio below, (11)

ENVIRONMENTAL CHEMICAL RISK ASSESSMENT

$$\text{AMR Risk Quotient} = \frac{\text{PEC}}{\text{PNEC}}$$

If PEC/PNEC > 1 unacceptable risk to the environment, institute risk reduction strategy
If PEC/PNEC < 1 no risk of AMR to the environment

On-site reduction of effluent antimicrobials should be a priority for manufacturers. They should implement risk mitigation and risk reduction strategies to reduce the site AMR risk quotient to less than one. The inspector should therefore check (and document) if any product(s) or material(s) have a AMR risk quotient (i.e. PEC/PNEC) that is greater than one.

The inspector should review:

- all the recommendations from the risk rating calculated, including all the risk reduction and/or risk control strategies developed by the manufacturer; and
- the periodic risk monitoring and verification strategy associated with preventing development of resistant microorganisms.

2.3 Premises

2.3.1 GMP/ Environmental Protection Requirements

"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". (12)*

2.3.2 Interpretation of requirements

Premises should be suited for the intended purpose. Premises for the manufacture of antimicrobial agents should be designed, constructed and maintained to ensure they aid in the prevention of microbial proliferation and plausible development of AMR inside the factory.

The design of premises should meet GMP requirements in terms of logical flow of materials, processes and personnel. This ensures that no mix-ups, cross-contamination and contamination occurs inside the factory.

The materials of construction of the factory i.e., walls, ceiling and floors, should be of appropriate material that allows ease of cleaning and decontamination and does not promote the growth of microbes exposed to antimicrobial agents for prolonged times.

2.3.3 Implications for inspector

The inspector should refer to the requirements in section 2.3.1 above and to the items in section 3.0 of the Aide-Mémoire and verify, among other things, that the premises provide the necessary containment to ensure protection of materials, products, operators and the environment.

The inspector should request for documentation for the factory floor layout diagrams and check for logical flow of materials, processes and personnel, including material airlocks (MAL), personnel airlocks (PAL), and change rooms/areas.

The inspector should observe if the floors, walls and ceilings throughout the facility are smooth, impervious and easy to clean and that there are no cracks or crevices where bacteria and fungi can lodge and proliferate.

2.4 Equipment

2.4.1 GMP Requirements

"Equipment must be designed, constructed, located, adapted, and maintained to suit the operations to be carried out. The layout and design of equipment must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of

2.4.2 Interpretation of requirements

Equipment used for the manufacturing and packaging of antimicrobial products in shared facilities should meet the GMP requirements in order to reduce the risk of antimicrobial resistance through cross-contamination that can result in medicines adulterated with traces of antimicrobial ingredients.

2.4.2.1 Appropriate design of the equipment

To permit effective cleaning and maintenance, the equipment used for the manufacture and packaging should be easy to disassemble with no recess areas "difficult-to-clean".

"Difficult-to-Clean" equipment surfaces/areas/sites include:

(a) Rough surfaces e.g. uneven, scratched, or otherwise damaged surface finish or improper weld seams.

(b) Plain surfaces with narrow or small cuttings, perforations, cavities, edges, folds, grooves, curves, corners, and angles.

(c) Narrow and small cylindrical tubes, square tubes, pipes, etc. (not hidden i.e. accessible).

(d) Threaded rods – solid or hollow, short or long.

(e) Wide or large hidden areas.

(f) Direct product-contact non-stainless-steel surfaces (glass, silicon, ceramic, aluminum, plastic polymers, etc.).

(g) Surfaces with deep and narrow corners, cuttings, perforations, cavities, edges, folds, grooves, curves, and angles.

(h) Narrow and long cylindrical tubes, square tubes, pipes, etc.

(i) Narrow or small hidden areas.

Closed-system processing is useful in minimising cross-contamination via contact with operator and the surroundings, but provide challenges for consistent adequate cleaning using the "visually-clean" criterion.

2.4.2.2 Suitable location of the equipment

Suitable placement of equipment for use, cleaning, sanitization and maintenance requires a location that minimizes risks of mix-ups and errors; prevents cross-contamination and dust and dirt build-up, and provides adequate space for maintenance.

2.4.3 Implications for inspector

The inspector should refer to the requirements in section 2.4.1 above and to the items in sections 4.0 of the Aide-mémoire and verify, among other things, that:

(a) Cleaning procedures are validated taking into consideration the product residues and the potential cumulative effect of multiple items of equipment in the process equipment train for the antimicrobial products manufactured and packaged at the site.

(b) Effluent and waste water from the equipment cleaning process is controlled to prevent contamination of the environment with antimicrobial residues. The aim should be not to exceed the maximum levels of antibiotic residues in an environmental matrix, below which resistance is unlikely to develop.

(c) Cleaning is performed according to the prescribed schedule, cleaning procedures (SOPs) are properly followed and documented at the time of performance, and cleaning records are available and comply with data integrity requirements (ALCOA principle).

2.5 Heating ventilation and air conditioning system

2.5.1 GMP/ Environmental Protection Requirements

"The HVAC system should be appropriately designed, taking into consideration the design of the facility, with various rooms or areas for storage of materials and in-process materials or products, processing, and movement of materials, products and personnel.

The required cleanliness classification should be achieved, as well as other parameters, such as air filtration, airflow velocity, air volumes, pressure differentials, temperature, relative humidity, viable and non-viable particle counts and containment. Conditions and limits should be determined and specified, based on need. These should be realistic, appropriate and scientifically justifiable at rest, in operation and as built at the time of design. In determining these, relevant factors and risks should be considered, including but not limited to possible failures of AHUs, seasonal variations, properties and types of materials and products, numbers of personnel and risks of cross-contamination". (13).

"Manufacturers should have controls in place to ensure that air from production areas, including contaminated air from equipment such as fluid bed driers, is passed through appropriate levels of filtration, to ensure that the environment is not polluted. Manufacturers should consult national and international environmental legislation". (13).

"Appropriate design and controls for the premise and HVAC systems should be in place to achieve containment, cleanliness and the appropriate level of protection of the product, personnel and the environment". (2).

2.5.2 Interpretation of requirements

Premises for the manufacture of pharmaceutical products should be supported by a well-designed, controlled and monitored HVAC system.

Before potentially product contaminated air from the process areas is discharged into the environment, it should be filtered to appropriate levels to prevent expelling antimicrobial agents into the environment. The level of filtration of exhaust air is dependent on the risk associated with the product.

The HVAC system should provide adequate differentiated pressures inside the plant to prevent cross-contamination and contamination.

Repairs, maintenance and preventive maintenance (including cleaning, replacement of components, changes, qualification) of HVAC systems should be executed in accordance with written procedures and records should be maintained.

2.5.3 Implications for inspector

The inspector should refer to the requirements in section 2.5.1 above and to the items in sections 5.0 of the Aide-Mémoire and verify, among other things, that there is an HVAC system in place with appropriate levels of filtration. This should be done through review of schematic drawings of the HVAC system and physical inspection of the Air Handling Units' areas.

The inspector should:

(a) verify that the exhaust filtration system design is sufficient to prevent contamination into and from the environment and air is filtered to appropriate levels before being discharged into the environment;

(b) check that the air pressurization design and balance is sufficient to prevent cross contamination between different products in shared facilities and that the HVAC system is well controlled, monitored and qualified on a regular basis; and

(c) review records related to the HVAC system monitoring and qualification.

2.6

Dust extraction and control

2.6.1 GMP Requirements

"Where dust is generated (e.g. during sampling, weighing, mixing and processing operations, or packaging of powder), measures should be taken to avoid cross-contamination and facilitate cleaning". (7).

"When dry materials and products are used in production, special precautions should be taken to prevent the generation and dissemination of dust. Provision should be made for proper air control (e.g. supply and extraction of air of suitable quality)". (7).

2.6.2 Interpretation of requirements

Dust extraction and control is important to prevent cross-contamination of antimicrobial products and controlling releases of antimicrobial dust into the environment.

Extracting dusts at their point of generation and conveying them to a correctly designed filtration system with in-built safety features is necessary to protect both personnel, plant and the environment. Any dusts that are generated from the production process must be extracted to ensure a safe, efficient and clean work area and to prevent cross-contamination.

Dust control is not only limited to the dusts that are generated during the production and packaging process and extracted at source, but includes cleaning of the production area and/or associated equipment.

2.6.3 Implications for inspector

The inspector should refer to the requirements in section 2.6.1 above and to section 6.0 of the Aide-Mémoire and verify, among other things, that dust controls are maintained to ensure product integrity and containment of antimicrobial products to prevent discharge into the environmen

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Aide-mémoire

Annex 1: Aide-mémoire

Waste management and prevention of cross-contamination to reduce the incidence of antimicrobial resistance areas to focus on during GMP Inspection

1.0 Particulars of inspected facility/site
1.1 Inspection reference number
1.2 Name of facility/site
1.3 Physical address of the site
1.4 Global positioning system coordinates
1.5 Activities carried out at the site
1.6 Type of inspection
1.7 Date(s) of inspection
1.8 GMP lead inspector(s)
1.9 GMP inspector(s)
1.10 Contact person(s) at inspected facility (names, designation, email)

2.0 Details of antimicrobial finished products and/or active pharmaceutical ingredients (APIs) manufactured at the facility/site	
Antimicrobial category	**Names of antimicrobial products / APIs manufactured**
Antibiotics	
Antivirals	
Antiparasitics	
Antifungals	

	Reference	Observational high level question	Applicable		Compliant			Documentation (Objective evidence) available[1]	Commentary	Rating (Critical/ Major/ Other)[3] see endnote
			Yes	No	Yes	No	WIP[2]			
1.0 Waste management	WHO TRS 957 Annex 3: section 4.1, 4.2	1.1 Are risk assessments done to determine if there are potential hazards to the operators and to the environment from antimicrobial substances contained in all types of waste?								
	WHO TRS 986 Annex 2: section 14.44, 14.45	1.2 Are waste material not allowed to accumulate (or overflow) and collected in suitable receptacles for removal to collection points outside the factory buildings?								
	WHO TRS 986 Annex 2: section 15.10	1.3 Are the waste collection receptacles covered and adequately identified? (e.g. labeled, colored?)								
	WHO TRS 986 Annex 2: section 16.11, 16.12(e)	1.4 Are operators properly wearing protective clothing during processing and packaging of antimicrobial products?								
		1.5 Are protective clothing contaminated with antimicrobial raw material or product kept in closed and labelled containers while awaiting cleaning?								
	WHO TRS 1019 Annex 2, section 10	1.6 Are there adequate measures taken to ensure that neither the antimicrobial product nor its residues are allowed to escape into the atmosphere or to be discharged directly to normal drainage systems?								
	WHO TRS 957 Annex 3: section 7.1, 7.2, 7.3, 13.1, 13.2	1.7 Are effluent and waste water from laundering of protective clothing (contaminated with antimicrobial raw material or product) neutralised, or made inert, before discharge to the effluent treatment plant or to the environment?								
		1.8 Are effluent and waste water from the cleaning of equipment and vessels used in the production and packaging of antimicrobial products controlled (treated e.g. neutralized or made inert) to prevent contamination of the environment and development of antimicrobial resistance?								

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	Reference	Observational high level question	Applicable		Compliant			Documentation (Objective evidence) available[1]	Commentary	Rating (Critical/ Major/ Other)[3] see endnote
			Yes	No	Yes	No	WIP[2]			
1.0 Waste management		1.9 Are the waste and waste water decontamination method(s) used adequate and effective in preventing the risk of antimicrobial resistance? (e.g. 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. Incineration may be considered for solid or semi-liquid waste).								
		1.10 Is there any effluent treatment plant and is it effective in deactivation of antimicrobial residues in solid and liquid waste effluent so as to protect the environment and prevent antimicrobial resistance?								
	WHO TRS 947 Annex 2, section 13.2;	1.11 Where external contractors are used for effluent disposal, do they have certification authorizing them to handle and treat hazardous products, including antimicrobial waste?								
	WHO TRS 1025 Annex 6	1.12 Has the manufacturer: • performed a vendor audit of the outsourced service providers (contracted companies); or • used contracted companies approved by the national environment management authority or other relevant national agencies/institutions; to ensure that adequate controls are in place and that there is no risk to contamination of the environment with antimicrobial waste?								

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	Reference	Observational high level question	Applicable		Compliant			Documentation (Objective evidence) available[1]	Commentary	Rating (Critical/ Major/ Other) [3] see endnote
			Yes	No	Yes	No	WIP[2]			
1.0 Waste management		1.13 What is the acceptable end-point for antibiotic treatment of antibiotic-containing waste?								
		1.14 Has the manufacturer determined the Predicted no-effect concentrations (PNECs) for the antimicrobial agents manufactured at site?								
		1.15 Has the post-treatment amount of antibiotics in the effluent been determined?								
2.0 Antimicrobial resistance site risk assessment	WHO TRS 1025 Annex 6 section 4	2.1 Is there documentation on 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?								
		2.2 Is there documentation on waste-stream analysis for each antimicrobial agent produced (at API sites and FPP sites)?								
		2.3 Is there documentation kept on 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?								
		2.4 Is the information on the methods used to treat the waste documented to be effective for each specific antimicrobial or antimicrobial precursor?								

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			Yes	No	Yes	No	WIP[2]			
2.0 Antimicrobial resistance site risk assessment		2.5 What are the PNECs for the antimicrobial agents manufactured at site? Are they PNEC-ENV or PNEC-MIC?								
		2.6 Has the site determined how much antimicrobial product is being exposed to the environment from the site? (Predicted Environmental Concentration-PEC?)								
		2.7 Has the site calculated AMR risk (PEC/PNEC) for all products and materials? Has the site identified any AMR risks greater than 1?								
		2.8 What risk mitigation measures are available to reduce the AMR risk characterization ratio/ risk quotient?								
3.0 Premises	WHO TRS 986 Annex 2: section 12.2	3.1 Does the design of the premises including positioning of equipment facilitate good containment relative to the type of products/materials handled? Particularly where there may be open handling of materials?								
		3.2 Are the premises designed for ease of cleaning or decontamination (e.g. to minimise collection points for powder that may be difficult to clean?)								
	WHO TRS 957 Annex 3: section 2.1	3.3 Are the facilities designed and operated in a way to protect the environment from contamination and thereby protect the public from possible harmful effects of products containing hazardous substances.								
	WHO TRS 986 Annex 2: section 12.27	3.4 Are there visible signs of loss of containment (e.g. powder on surfaces of equipment, walls, floors, or lack of primary containment?)								

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			Yes	No	Yes	No	WIP[2]			
3.0 Premises	WHO TRS 986 Annex 2: section 12.10	3.5 Do personnel flow charts, and general flow charts for each manufacturing process not reveal a risk of cross-contamination?								
		3.6 Is the movement of any person, irrespective of position or purpose of entering in different production areas processing different antimicrobial products, controlled to prevent cross-contamination?								
	WHO TRS 986 Annex 2: section 12.12	3.7 Are changing rooms well designed, equipped & appropriately used?								
		3.8 Are Entry & Exit procedures into changing rooms and controlled production and packaging areas followed?								
	WHO TRS 986 Annex 2: section 12.6, 12.17	3.9 Are the premises cleaned and maintained in accordance with SOPs and records maintained?								
4.0 Equipment	WHO TRS 986 Annex 2: section 13.1	4.1 Is the equipment designed to facilitate ease of cleaning and confirmation of cleanliness (e.g. visual inspection, swabbing)?								
	WHO TRS 986 Annex 2: section 13.12, 15.31(a), 15.35,	4.2 Is there an adequately detailed procedure(s) for campaign change-over including cleaning of product-contact parts, cleaning of non-product contact surfaces e.g. AHU, exterior of equipment, walls, ceilings, floors?								
	WHO TRS 986 Annex 2: section 19.9, 15.37(c)	4.3 Are sampling and dispensing tools adequately cleaned and properly status-labelled?								

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			Yes	No	Yes	No	WIP[2]			
4.0 Equipment	WHO TRS 986 Annex 2: section 13.6	4.4 Is cleaning of all the equipment in the equipment train done on schedule?								
	WHO TRS 986, Annex 2: section 4.4, 4.11, 13.8, 13.12, 15.23(f), 15.46, 15.48	4.5 If Clean-In-Place (CIP) or Clean-Out-of-Place (COP) systems are utilized (e.g. skids for vessel cleaning, or machine parts), are they appropriately designed?								
		4.6 Are CIP/COP cycles adequately specified, monitored, recorded and reviewed?								
		4.7 Are difficult-to-clean and hard-to-clean parts of equipment adequately identified?								
		4.8 Do the cleaning procedures provide instructions for disassembling and re-assembling each article of equipment to ensure complete removal of product residues especially on Difficult-to-Clean, and Hard-to-Clean surfaces (e.g. by brushing, scrubbing, or using pressurised water or compressed air to dis-lodge product residue particles)?								
		4.9 Were the cleaning procedures established on the basis of the results of the cleaning validation performed?								
		4.10 Are the cleaning procedures followed and records available?								
		4.11 Have mobile or fixed equipment/accessories been identified and is equipment cleaning status clear and secure to prevent mix-ups and error? Is the process adequately documented (status labels, logbooks)?								

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			Yes	No	Yes	No	WIP[2]			
4.0 Equipment		4.12 Are dedicated equipment/parts (e.g. bag filters for fluidized bed drier) clearly labelled and controlled appropriately?								
		4.13 Do the production plans for campaign manufacture in shared facilities provide adequate measures to prevent cross contamination? (e.g. during product change-over)								
		4.14 Is movement of ancillary equipment (e.g. In-process control test equipment) & materials between different products & areas adequately controlled?								
		4.15 Do manual cleaning & clean-out-of- Place processes adequately define the level of disassembling of equipment required for consistent application?								
		4.16 Are diagrams or pictures illustrating disassembled equipment used to support consistent, reproducible and error-free cleaning?								
		4.17 Are the tools used in equipment disassembly, reassembly and cleaning, subject to adequate control so that they are not potential sources of contamination from the antimicrobial product/material?								
		4.18 Is the visual inspection process, where applicable, clearly described and conducted in a manner to ensure potential contaminants (e.g. residues) are seen?								
		4.19 Are appropriate methods and tools used to help detect residues by visual inspection (e.g. use of beam light, mirror or magnifying glass, telescopic gadgets) adequately defined in the cleaning procedure?								
	WHO TRS 986 Annex 2 section 2.1(c)(l), 9.2	4.20 Have the persons performing the visual inspection of cleaned equipment been properly trained and qualified? (verify records)								

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			Yes	No	Yes	No	WIP[2]			
4.0 Equipment	WHO TRS 986 Annex 2: section 15.26	4.21 Is the person conducting the final visual inspection of a cleaned equipment, or vessel, adequately independent of the cleaning operation?								
	WHO TRS 986 Annex 2: section 1.5(s),16.3	4.22 Are there records of actions taken (e.g. deviations) in case of failures in cleaning such as: (a) Where execution of the prescribed cleaning instruction has failed to render the equipment clean, (b) Where, upon visual inspection by an independent person, the equipment is found not to be clean, or (c) When swab or rinse samples fail?								
		4.23 Are all deviations related to cleaning investigated and taken into consideration during the periodic review of cleaning validation/verification?								
5.0 HVAC System and environmental protection against AMR	WHO TRS 1010, Annex 8	5.1 Are the HVAC systems, including AHUs for equipment like Fluid Bed Dryer, Auto-coater, validated (performance qualification reports)?								
		5.2 Is re-validation of the HVAC systems done on a regular basis e.g. annually?								
	WHO TRS 1019, Annex 2	5.3 Are the HVAC schematic diagrams, including zoning design and associated AHUs, pressure cascades and air flows appropriate in the prevention of cross-contamination?								
		5.4 Do the designed air flows take account of occurrences such as operation of local dust extraction (de-dusting) units, vacuum transfer systems and doors opening?								
		5.5 Are the pressure differentials within limits?								
		5.6 Are critical AHUs like the corridors and room AHUs interlocked?								

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		5.7 Are HEPA filters (e.g. EU 9 of 0.3µ) used in the exhaust filter unit for the AHUs for the areas processing antimicrobial products (e.g. exhaust air from the fluidized-bed driers)?								
6.0 Dust extraction and control	WHO TRS 986 Annex 2: section 12.3, 12.23, 13.1, 16.10; and WHO TRS 1019 Annex 2, section 9	6.1 Are there appropriate de-dusting and/or dust extraction systems that extract dust at the source (e.g. during sampling, weighing, mixing and processing operations, or packaging of powder)?								
	WHO TRS 957 Annex 3: section 11.5, 11.6, 11.7	6.2 Are checks for dust build-up in the dust conveying tube performed at regular intervals? (check records e.g. logbooks, for frequency of checks)								
		6.3 Is the monitoring of filters done at regular intervals to prevent excessive filter loading that could force dust particles through the filter media, or could cause the filters to burst, resulting in ambient contamination?								
	WHO TRS 957 Annex 3: section 11.14	6.4 Is there an appropriate room of adequate size (e.g. room under negative pressure relative to the environment), with suitable equipment and procedure for the cleaning, or the removal of antimicrobial dust, from pre-filters and portable vacuum cleaners?								
		6.5 Are terminal filters in the dust exhaust system appropriate to prevent contamination of the atmosphere? Are the filters changed on schedule? (The final filters on exhaust air unit should be HEPA filters, e.g. at least an EU 9 of 0.3µ, 95% efficient)								

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6.0	WHO TRS 957 Annex 3: section 11.12	6.6 Are all exhaust points outside the building located as far as possible from air entry points?								
	WHO TRS 957 Annex 3: section 11.15	6.7 Are records of safe disposal of all antimicrobial-contaminated filters (e.g. HEPA filters) and dust kept?								

[3] Rating of deficiencies

Critical deficiency

A deficiency may be classified as ***critical*** if it has produced, or may result in a significant risk of producing, a product that is harmful to the human or veterinary patient or a product which could result in a harmful residue in a food producing animal.

Major deficiency

A deficiency may be classified as ***major*** if it:

- has produced or may produce a product that does not comply with its marketing authorization; or
- indicates a major deviation from GMP; or
- indicates a failure to carry out satisfactory procedures for release of batches; or
- indicates a failure of the person responsible for quality assurance/quality control to fulfil his or her duties; or
- consists of several other deficiencies, none of which on its own may be

Other deficiency

A deficiency may be classified as ***other*** if it cannot be classified as either critical or major but indicates a departure from GMP. A deficiency may be other either because it is judged to be minor or because there is insufficient information to classify it as major or critical.

Note: Classification of a deficiency is based on the assessed risk level and may vary depending on the nature of the products manufactured, e.g. in some circumstances an example of an "other" deficiency may be categorized as a "major" deficiency.

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