Annex Five (5)

ANNEX 5: GOOD MANUFACTURING PRACTICE GUIDELINE FOR MUTUAL RECOGNITION PROCEDURES

FOR THE REGISTRATION OF VETERINARY ECTOPARASITICIDES PRODUCT(S) IN THE EAST AFRICAN REGION

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INTRODUCTION

Manufacture of veterinary medicinal products involve operations of purchase of materials, production, quality control, release, storage, shipment of finished products and the related controls. Such operations need to be carried out according to Good Manufacturing Practices (GMP) that forms an important part of a comprehensive system of quality assurance. Adherence to GMP ensures that veterinary medicinal products are manufactured to meet quality standards required for their intended use.

In order to protect the animals and public against health hazards associated with the use of medicines and cope with advancement in medicinal products sciences and technology, EAC MRP has developed GMP guidelines for veterinary medicinal products.

This guideline highlights in detail the principles of GMP that should be followed by all companies involved in any aspect of manufacturing of veterinary medicinal products for veterinary use. The guidelines targets both Regional and foreign manufacturers who intend to obtain marketing authorization in EAC and shall form the basis for licensing veterinary medicinal products manufacturers in the region. This is in line with the requirements of the EAC Partner States legal frameworks.

The document is divided into chapters and annexes. Chapter one (1) to fifteen (15) delineate the principles, general considerations and requirements for quality management, personnel, sanitation and hygiene, premises, equipment, material, documentation, good practices in production, good practices in quality control, contract production and analysis, complaints and product recalls, self-inspection and quality audits, qualification and validation, heating, ventilation, and air conditioning (HVAC) system and water treatment.

Annex one (1) of the document illuminates GMP requirements to produce sterile veterinary medicinal products. This additional guidance has been provided to minimize the risks of microbiological, particulate and pyrogen contamination during manufacturing of sterile veterinary medicinal products.

Annex two (2) outlines GMP requirements to produce veterinary biological products. Unlike conventional pharmaceutical products which are normally produced and controlled by means of reproducible chemical and physical techniques, biological products are manufactured with biological materials and processes, such as cultivation of cells or extraction of materials from living organisms. As such materials and processes display inherent variability and the range and nature of manufacturing by-products in biological products are likewise variable. For such products, including vaccines, hormones and enzymes, full adherence to the GMP guidelines is recommended for all production steps, including those from which active ingredients are produced.

Annex three (3) Outline GMP requirements to manufacture *medicated feeding stuff* as any mixture of a veterinary medicinal product or products and feed or feeds which is ready prepared for marketing and intended to be fed to animals without further processing because of its curative or preventative properties or other properties (e.g.,

medical diagnosis, restoration, correction, or modification of physiological functions in animals):

Annex four (4) outline GMP requirement for manufacture of liquids, creams, and ointments. Liquids, creams, and ointments may be particularly susceptible to microbial and other contamination during manufacture. Therefore, special measures must be taken to prevent any contamination.

Annex Five (5) Outlines GMP requirement for production of (Veterinary pesticides) ectoparasiticides for external application to animals, which are veterinary medicinal products, and subject to marketing authorization. Ectoparasiticides are those products applied externally to animals to control only external parasites. Ectoparasiticides differ from most other veterinary chemical products in that they contain pesticides that may be toxic and generally incompatible with other forms of medicinal products. Consequently, ectoparasiticides should not be manufactured in the same area as other veterinary chemical products unless special precautions are taken to prevent cross-contamination. These precautions might include the use of dedicated equipment that is adequately separated from other processing areas or, where the same equipment is to be used for incompatible products, the use of scheduling and validated cleaning procedures.

The requirements set forth in these guidelines should be considered as minimum and they are not meant to replace other legal controls, but rather to complement or supplement them.

ANNEX 5 Ectoparasiticides

1. Introduction

Ectoparasiticides are products applied externally to animals to control /ectoparasites. This annex is set to guide good practices applicable to facilities handling ectoparasiticides that contain hazardous substances such as certain inflammable, toxic, explosives, corrosives irritants. They do not replace national legislation for protection of the environment and personnel. The Annex and the main GMP guides to good manufacturing practices (GMP) and regulations need to be observed in addition to the workers' safety criteria, dangerous goods and hazardous substances legislation. The national laws that may govern special storage condition for goods that are of a dangerous or hazardous nature should be complied with.

Ectoparasiticides differ from most other veterinary chemical products in that they contain poisonous active substances that may be toxic and generally incompatible with other forms of medicinal products.

Consequently, ectoparasiticides should not be manufactured in the same area as other veterinary chemical products unless special precautions are taken to prevent cross-contamination. These precautions might include the use of dedicated equipment that is adequately separated from other processing areas, or, where the same equipment is to be used for incompatible products, the use of scheduling and validated cleaning procedures should be employed. Because some of the active substances are also used for agricultural chemicals, ectoparasiticides are occasionally manufactured in plants/facilities that also make agricultural chemicals. In those circumstances, rigorous precautions need to be taken to eliminate the risk of cross-contamination with pesticides, herbicides and incompatible materials.

This annex is to be read in conjunction with EAC MRP GMP guidelines with respect to building finishes and general services installations, among others. The primary focus of this annex is on the air-conditioning and ventilation systems of the facility; however, the document also provides some guidance on personnel protection.

Some of the products such as ectoparasiticides (acaricides) for dipping, are made in large volumes using solvents and other materials that are highly inflammable that are stored in drums or specially constructed storage vessels. Outdoor storage of such materials may be acceptable, provided storage conditions such as temperature are appropriate for the materials involved. Safety issues, such as the explosion hazard of excessive dust generation and the possibility of inhalation of chemical laden dust by personnel (e.g. organophosphate pesticides), should be considered in the design and location of ectoparasiticides manufacturing plant.

The areas to which this annex applies include all zones where the handling of products could lead to cross-contamination, exposure of personnel, or discharge to the environment. These includes the sites of active substance manufacturing, formulated product manufacturing and storage.

Where possible products should be manufactured in closed systems.

2. General

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

2.1. To ensure quality of ectoparasiticide products;

2.2. To protect the operators from possible harmful effects of ectoparasiticide products containing hazardous substances; and

2.3. To protect the environment from contamination and thereby protect the public from possible harmful effects of ectoparasiticide products containing hazardous substances.

2.4. The production of ectoparasiticides products involve hazardous substances that should generally be conducted in separate, dedicated, self-contained facilities.

These self-contained facilities may be in the same building as other facilities but should be separated by a physical barrier and have, e.g. separate entrances, staff facilities and air-handling systems. The extent of the separation from adjacent facilities and sharing of common services should be determined by risk assessments.

In general, these manufacturing facilities should be regarded as containment facilities.

3. Buildings and Grounds

As a general rule, ectoparasiticides should not be manufactured in the same area as other veterinary chemical products. They should be made in segregated areas or separate buildings, using equipment that is dedicated to this type of product. However, use of common equipment may be accepted, if cross-contamination is controlled by scheduling and use of a validated cleaning procedure.

Similarly, where ectoparasiticides are manufactured in a facility that also manufactures agricultural chemicals, they should be made in a separate area of the facility, using equipment dedicated to veterinary chemical manufacture. Special measures are needed to prevent cross-contamination with agricultural chemicals, particularly where shared facilities, such as packing rooms, are used.

The effective operation of a facility may require the combination of some or all of the following aspects:

3.1. Appropriate facility design and layout, with the emphasis on safely containing the materials being handled. Manufacturing processes using closed systems or barrier technology enhance operator and ectoparasiticide product protection;

3.2. Manufacturing process controls including adherence to standard operating procedures (SOPs);

3.3. Appropriately designed environmental control systems (ECS) or heating, ventilation and air-conditioning (HVAC);

3.4. Extraction systems;

3.5. Personal protective equipment (PPE);

3.6. Appropriate degowning and decontamination procedures;

3.7. Industrial hygiene (monitoring staff exposure levels);

3.8. Medical surveillance (monitoring staff exposure levels); and

3.9. Administrative controls.

3.10. Adequate validated cleaning procedures should be employed to prevent cross contamination, and steps should be taken to ensure the secure storage of the veterinary pesticide product in accordance with the guide.

3.11. Bunding may be required in some situations to meet the requirements of dangerous goods and environment protection legislation.

3.12. Outside storage of high-volume materials (e.g. solvents in 200 litre drums) may be acceptable, provided they are in adequately sealed containers and outside storage conditions are unlikely to adversely affect their quality.

4. Facility Layout

The premises should be designed and constructed to prevent the ingress or egress of contaminants. While designing the facility, attention should be paid to the level of containment provided by the equipment.

4.1. The link between the interior and exterior of the premises should be through airlocks (PAL and/or MAL), changing rooms, pass boxes, pass-through hatches, decontamination devices, etc. These entries and exit doors for materials and personnel should have an interlock mechanism or other appropriate system to prevent the opening of more than one door at a time.

4.2. The changing rooms should have an arrangement with a step-over-bench. The facilities on the exit side should incorporate showers for the operators.

4.3. The premises should be laid out and designed so as to facilitate the required pressure cascades and containment.

4.4. The premises (and equipment) should be appropriately designed and installed to facilitate cleaning and decontamination.

4.5. The manufacturing site and buildings should be described in sufficient detail (by means of plans and written explanations) to ensure that the designation and conditions of use of all the rooms are correctly shown.

4.6. The flow of people and ectoparasiticide products should be clearly marked on the layouts and plans.

4.7. The activities carried out in the vicinity of the site should be indicated.

4.8. Plans should describe the ventilation systems, indicating inlets and outlets, in relation to other facility air inlet and outlet points.

4.9. The facility should be a well-sealed structure with no air leakage through ceilings, cracks or service areas.

4.10. Areas of the facility where exposed ectoparasiticide product presents a risk should be maintained at a negative air pressure relative to the environment.

5. Personnel Decontamination Systems

5.1. The risk of exposures to ectoparasiticide's poisoning in the manufacturing plants, should be reduced by providing workers with clear instructions and guidelines for handling and disposing of ectoparasiticides, and to regularly review and update safety procedures to ensure they are effective and up to date.

5.2. Any production activities (including weighing, milling, or packaging) of highly toxic ectoparasiticidal materials such as herbicides and pesticides should not be conducted using the buildings and/or equipment being used to produce APIs. Handling and storage of these

highly toxic nonpharmaceutical materials should be separate from other non-related products

5.3. If required, a means of preventing contaminants from leaving the facility on the garments of personnel should be provided. This could be in the form of an air shower; mist shower, water shower or appropriate device.

5.4. Appropriate air shower comprising of correctly fitted airlock where high velocity air is supplied through air nozzles (e.g. from the sides of the airlock) should be installed in order to dislodge dust particles. Air extraction grilles (e.g. at low level) should draw the air away and return it to the filtration system. Some air showers may also incorporate a vertical unidirectional airflow section at the exit end, to flush contaminants away.

5.5. An air shower comprises an airlock where high velocity air is supplied through air nozzles (e.g. from the sides of the airlock) in order to dislodge dust particles. Air extraction grilles (e.g. at low level) should draw the air away and return it to the filtration system. Some air showers may also incorporate a vertical unidirectional airflow section at the exit end, to flush contaminants away.

Note: When air showers are used these should be correctly designed to effectively extract dust.

5.6. Air filtration of the supply air and return or exhaust air should comply with the same filtration standards as used in the manufacturing facility. Normally the fan should be activated by opening the door as the operator enters the shower, with a timing device on the exit door interlock to allow sufficient time for the decontamination process to be effective.

5.7. Flushing devices similar to air or mist showers for personnel could be used at material exits to assist with removing contaminants.

5.8. Wet mist or fog decontamination systems for operators can be employed for deactivating contaminants on the operator's garments, or causing contaminants to adhere to the garments so that they are not easily liberated.

5.9. Personnel should change into clean garments after showering.

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6. Personal Protection Equipment and Breathing Air Systems

The fundamental design principle for a facility and its production equipment is to provide product containment and operator protection. If the facility and equipment design does not provide adequate ectoparasiticide product containment, operator protection should be provided. Unless otherwise specified in the material safety data sheet, operators should be protected from exposure with an appropriate method, such as by wearing:

6.1. Flash-spun, high-density polyethylene fibre material suits or impervious washable protective suits. Integral hoods may be required depending on the respirator type used;

6.2. Flash-spun, high-density polyethylene fibre material shoes, lower leg covers or cleanable boots;

6.3. Suitable single-use, disposable gloves. Double gloves should be worn where direct active contact with the ectoparasiticide product cannot be avoided. Gloves should be taped or sealed on to the protective suit sleeves; and

6.4. Respirator eye and face protection with associated breathing air systems.

6.5. Where breathing air systems are used, these should be provided to supply safe breathing air to the operators to prevent them from inhaling air from within the facility. Personnel should be appropriately trained and assessed in the use of these systems before they can enter the area. The breathing air systems should comprise a protective face mask, which should form an integral part of a protective suit. The breathing air systems could be any of the systems described below:

6.6. A central air supply system which connects to the operator's face mask by means of flexible hoses and quick coupling sockets, also called an airline respirator (AR). The air connection should incorporate a one-way air system to prevent contaminated air entering the face mask during connection or disconnection. The air supply should be treated to ensure a temperature and level of humidity that are comfortable for the operator. The air source could be a high-pressure fan or an air compressor. If an air compressor is

used, it should be of the oil-free type or have suitable oil removal filters fitted;

6.7. A self-contained breathing apparatus (SCBA) or powered air purifying respirator (PAPR) that is securely attached to the operator's belt and connects to the operator's face mask. This system draws air from the room in which the operator is working and the air supply is delivered to the face mask by means of a battery-driven fan. The AR provides superior protection to the PAPR apparatus;

6.8. For zones with lower contamination levels, a half-mask high efficiency particulate air filter (HEPA) cartridge respirator of N95-type paper filter mask may be acceptable.

6.9. The selection of the respirator type is based on the relationship between the accepted OEL and the respirator-certified protection factor (PF).

6.10. The air supplies should be filtered through a final filter, which should be a HEPA filter rated as an H13 filter according to EN 1822 (European Norm). The supply of breathing air into the face mask and/or protective suit should result in the interior of the mask and suit being at a positive pressure relative to the facility environment.

Central breathing air supply systems should have a 100% back-up system in the event of the main system failing. This could be in the form of a gas bottle system with at least 5 minutes supply. Changeover from the normal supply to the back-up supply should be automatic. The system should have a monitoring system and send alarm signals to a permanently manned location in the following situations:

6.11. Failure of main air supply;

6.12. Temperature out of specification (OOS);

6.13. Humidity OOS;

6.14. Carbon dioxide (CO2) OOS;

6.15. Carbon monoxide (CO) OOS; and

6.16. Sulfur dioxide (SO2) OOS.

6.17. Breathing air should be filtered by means of pre-filters, coalescing filters and final filters to have the minimum air quality specifications

of ISO 8573-1 3-9-1 and EN 12021:1999.

6.18. Where air is delivered through a central system the piping should not cause

6.19. Any contamination to be liberated into the air stream. Stainless steel piping is preferred. The final filters should be as close as possible to the operator connection points. The operator hose connection to the air supply should be a dedicated connection specific to the breathing air system (to avoid inadvertent connection to a different gas system).

7. Environmental Protection

Due to the hazardous nature of the ectoparasiticides 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 before pretreatment.

7.1. Thermal destruction is generally used, when toxic and carcinogenic chemicals are emitted from the process.

7.2. Conversion of organic pollutants to harmless product before they are released to the environment

7.3. Combination approach may be applied while cleaning of pipe gases can combine both recovery and reduction as appropriate.

7.4. The external environment and the public in the vicinity of the facility should be protected from possible harm from hazardous substances emissions.

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

8. Safe Change Filter Housings

Safe change or bag-in-bag-out filter housings should be suitably designed to provide operator protection and to prevent dust from the filters entering the atmosphere when filters are changed.

8.1. The final filters on the safe change unit should be HEPA filters with at least an H13 classification according to EN 1822 filter standards. For dusty return, air pre-filtration may also be required to prolong the life of the HEPA filters. The pre-filtration filters should also be

removable through the bag-in-bag-out method.

8.2. For exhaust systems where the discharge contaminant is considered particularly hazardous, two banks of HEPA filters with adequate and correct separation techniques must installed to provide additional protection should the first filter fail.

8.3. All filter banks should be provided with pressure differential indication gauges to indicate the filter dust loading and remaining lifespan of the filters. Connection to these gauges should be copper or stainless steel and not plastic tubing, which could perish causing a contamination hazard. The tube connections on the filter casing should be provided with stopcocks, for safe removal or calibration of gauges.

8.4. Monitoring of filters should be 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 air contamination.

8.5. Computer-based data monitoring systems may be installed to monitor filter condition.

8.6. Filter pressure gauges should be marked with the clean filter resistance and the change-out filter resistance.

8.7. Installed filter leakage tests should be performed in accordance with ISO 14644-3. Injection ports (upstream) and access ports (downstream) should, therefore, be provided for this purpose.

8.8. The exhaust air fan on a safe change filter system should be located after the filters so that the filter housing is maintained at a negative pressure. This poses a difficulty when carrying out filter integrity tests, and for this reason a bypass damper system should be provided, so that air can be circulated through the HEPA filters, while the scanning ports are open. Alternatively, an independent booster fan system can be used, with appropriate shut-off dampers. The bypass arrangement permits decontamination of the filters by means of circulation of a sanitizing agent.

8.9. All exhaust systems from the facility, including dust extraction systems, vacuum system exhaust, fluid bed drier exhaust and

coating pan exhaust, should be passed through safe change filter housings fitted with relevant separation techniques before being exhausted to the atmosphere.

8.10. All exhaust points outside the building should be located as far as possible from air entry points, and exit points should be at a high level to minimize the possibility of re-entrainment of exhaust air. Dominant and seasonal wind directions should be taken into account when positioning exhaust and supply points.

8.11. Where excessively dust-laden air is handled, a dust collector or bag house should be considered, with the dust collector being located in an enclosed room maintained at a negative pressure. Access control, maintenance staff, personal protection equipment (PPE) and breathing air systems should then be provided to protect the operators during removal of dust from the collector bins.

8.12. Portable vacuum cleaners and portable dust collectors should be fitted with H13 HEPA filters. These types of units should be emptied and cleaned in a room which is under negative pressure relative to the environment. Personnel should be provided with suitable PPE.

Records of the safe disposal of all contaminated filters and dust should be kept.

9. Effluent Treatment

Liquid, gaseous and solid waste effluent should be handled in such a manner as not to present a risk of contamination to the ectoparasiticide product, personnel or to the environment. Separations techniques should be applied depending of the type of effluent released in the manufacturing facility before they can safely be released.

- Gas solid separation
- Liquid-liquid separation
- Gas liquid separation
- Conversation to harmless end product
- Thermal destruction

9.1. 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.

9.2. Ectoparasiticides can pose various health and environmental hazards. Some of the hazards associated with these chemicals include toxicity, flammability, corrosiveness, irritancy, and explosiveness. It is essential to understand the hazards associated with each chemical and take appropriate safety measures to protect oneself, other people, livestock, and the environment.