MCAZ Medicines Control Authority of Zimbabwe

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GOOD MANUFACTURING PRACTICE (GMP) GUIDELINE FOR VETERINARY PRODUCTS (ECTOPARASITICIDES)

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1.0 APPLICATION

This Good Manufacturing Practice (GMP) guideline applies to;

1.1 Prospective and licensed ectoparasiticide manufacturers in Zimbabwe.

1.2 Inspection of international ectoparasiticide manufacturers who have products registered with the Authority or intend to register their products with the Medicines Control Authority of Zimbabwe.

2.0 PURPOSE

To outline the minimum GMP requirements for the manufacture of Ectoparasiticides, with the aim of ensuring that such products are of good quality, efficacy and are safe for use.

3.0 BACKGROUND/INTRODUCTION

Veterinary ectoparasiticides are subject to a registration process that requires them to be fit for their intended use and to not place treated animals or users at risk due to inadequate safety, quality, or efficacy. Veterinary ectoparasiticides must be manufactured in such a way that they comply with their registered particulars and that there is batch-to-batch consistency. To achieve these objectives, the manufacturer must have in place a comprehensively designed, adequately resourced and correctly implemented system of quality assurance, incorporating the principles of good manufacturing practice (GMP). Against this background, these guidelines were drafted to assist manufacturers of veterinary ectoparasiticides and MCAZ GMP Inspectorate to have a common reference source. This will allow manufacturers to proactively assess their compliance to cGMP and ensure that products marketed in Zimbabwe are safe, efficacious and of the right quality.

For further clarification on this subject matter, please contact the MCAZ GMP Inspectorate on the following:

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4.0 DEFINITIONS

4.1 **Ectoparasiticides** are those products applied externally to animals to control only external parasites. Ectoparasiticides differ from most other veterinary medicinal products in that they contain pesticides that may be toxic and generally incompatible with other forms of medicinal products (APVMA Annex 5, 2007).

4.2 **Manufacture** includes compounding, processing or packaging for sale but does not include the compounding of a medicine by a medical practitioner, dental practitioner, veterinary surgeon, or pharmacist if that medicine ─

4.2.1 has not been advertised for sale in Zimbabwe; and

4.2.2 does not contain any component the sale of which is prohibited by this Act; and 4.2.3 is supplied for the treatment of a particular person or animal; (MASCA 15:03)

Manufacturer is a company that carries out operations such as production, packaging, repackaging, labelling, and relabelling of pharmaceuticals (WHO TRS986 Annex 2) and should be licensed in terms of section 55(2) of the Medicines and Allied Substance Control Act.

4.3 **Contamination** is the undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or on to a starting material or intermediate during production, sampling, packaging, or repackaging, storage or transport (WHO TRS986 Annex 2).

4.4 **Medicine**, subject to section seventy-five of the amended Act 6/2000, means any substance or mixture of substances which is used, or is manufactured, sold, or represented as suitable for use, in—

The diagnosis, treatment, mitigation, or prevention of disease or any abnormal physical or mental state or the symptoms thereof in man or in animals; or

Restoring, correcting, or modifying any physical, mental, or organic function in man or in animals (MASCA: 15:03)

4.5 **Pharmaceutical product** is any material or product intended for human or veterinary use presented in its finished dosage form, or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in the exporting state and/or the importing state (WHO TRS986 Annex 2).

4.6 **Cross-contamination** is contamination of a starting material, intermediate product or finished product with another starting material or product during production (WHO TRS986 Annex 2).

4.7 **Quality assurance** is a wide-ranging concept covering all aspects of the manufacturing process that individually or collectively influence the quality of a manufactured product. It is the sum of the arrangements made to ensure that veterinary medicinal products are consistently manufactured in an appropriate manner to the quality standards required for their intended use.

4.8 **Good manufacturing practice** (GMP) is the part of quality assurance that ensures that products are consistently manufactured to the quality standards appropriate for their intended veterinary use and in accordance with their registration particulars and specifications. GMP is concerned with both production and quality control. It is a means of giving consumers confidence that the products meet the required quality standards and are safe and reliable for the purposes for which they are intended.

4.9 **Quality control** is the part of GMP that is concerned with specifications, sampling, and testing, and with the organisation, documentation and release procedures that ensure that the necessary and relevant tests are carried out so that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory. Compliance with GMP ensures that quality is built into the product at the time of manufacture. It requires products to be consistently manufactured in a safe and clean environment, by specified methods, under adequate supervision, with effective quality control procedures, and with a documentation trail that links starting materials, through the various manufacturing processes, to the finished product.

5.0 GUIDELINES

5.1 Quality Management

5.1.1 Manufacturing principles

Manufacturers of ectoparasiticides must have in place a quality assurance system to ensure that finished products are fit for their intended use, comply with registration requirements, and do not place treated animals or users at risk due to inadequate quality, safety, or efficacy.
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. Because some of the active materials are also used for agricultural chemicals, ectoparasiticides are occasionally manufactured in plants 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.

Some of the products such as sheep dips, are made in large volumes using solvents and other materials that are sometimes 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 manufacture.

The quality assurance system must ensure that:

i. appropriate procedures are in place to ensure that relevant quality standards are met,
ii. all materials involved in the manufacturing process comply with required quality standards before they are released for use in manufacture,
iii. there are measures designed to prevent cross-contamination,
iv. there are safeguards and controls in place designed to prevent the occurrence of foreseeable errors or process failures,
v. finished products have been made and stored correctly, and they comply with required quality standards before they are released for supply.

vi. The quality assurance system must be relevant to the nature and intended use of the product. It must be fully documented, monitored for effectiveness and provide for continuous improvement.

Ectoparaciticides must be manufactured in buildings that are located, designed, constructed, maintained, and utilised to:

i. suit the operations carried out in them,
ii. ensure protection of the ectoparasiticides from contamination,
iii. permit effective cleaning and maintenance, including cleaning after processes have been completed,
iv. minimise the risk of manufacturing error.

The products must also be manufactured in an environment, or in equipment fitted with precautionary measures, that:

i. ensures a standard of hygiene appropriate to the class of ectoparasiticides being manufactured,
ii. minimises the risk of cross-contamination of the finished product, or of materials or components that are used or manufactured at the premises,
iii. ensures the safety of operators and protects the outside environment.
iv. Manufacturing processes that involve the application of a liquid premix onto an inert carrier powder should ensure adequate dispersion of the liquid and, therefore, the active ingredient(s). Mixing times and methods should ensure batch homogeneity.
v. Measures should be in place to prevent cross-contamination from hoses, fixed pipework and connections.

5.1.2 Quality Management System

An appropriate infrastructure or quality system, encompassing the organizational structure, procedures, processes and resources should be in place. The quality system should be defined and documented. A quality manual or equivalent documentation should be established and should contain a description of the quality management system including management responsibilities.

There should be periodic management reviews, with the involvement of senior management, of the operation of the quality system to identify opportunities for continual improvement of products, processes and the system itself. Unless otherwise justified, such reviews should be conducted at least annually.The quality system appropriate to the manufacture of veterinary products should ensure the following:

5.1.2.1 product realization is achieved by designing, qualifying, planning, implementing, maintaining and continuously improving a system that allows the consistent delivery of products with appropriate quality attributes;

5.1.2.2 product and process knowledge is managed throughout all lifecycle stages;

5.1.2.3 veterinary products are designed and developed in a way that takes account of the requirements of GMP and other associated codes such as those of good laboratory practice (GLP) and good clinical practice (GCP);

5.1.2.4 production and control operations are clearly specified in a written form and GMP requirements are adopted;

5.1.2.5 managerial responsibilities are clearly specified in job descriptions;

5.1.2.6 arrangements are made for the manufacture, supply and use of the correct starting and packaging materials, the selection and monitoring of suppliers and for verifying that each delivery is the correct material from the approved supply chain;

5.1.2.7 all necessary controls on starting materials, intermediate products, and bulk products and other in-process controls, calibrations and validations are carried out;

5.1.2.8 the finished product is correctly processed and checked, according to the defined procedures;

5.1.2.9 pharmaceutical products are not sold or supplied before the authorized persons have certified that each production batch has been produced and controlled in accordance with the requirements of the marketing authorization and any other regulations relevant to the production, control and release of pharmaceutical products;

5.1.2.10 processes are in place to assure the management of outsourced activities;

5.1.2.11 satisfactory arrangements exist to ensure, as far as possible, that the veterinary products are stored, distributed and subsequently handled so that quality is maintained throughout their shelf-life;

5.1.2.12 there is a procedure for self-inspection and/or quality audit that regularly appraises the effectiveness and applicability of the quality system. Manufacturers of ectoparasiticides must regularly and systematically carry out internal audits of all aspects of their manufacturing operations, as well as of their quality assurance program, in order to monitor compliance with their authorised procedures, standards and requirements and ensure product quality. Steps must be taken to implement any necessary corrective and preventive action identified by those internal audits and to assess the outcomes;

5.1.2.13 A program of planned and documented internal audits (self-inspections) should be in place to assess all aspects of manufacture and quality control regularly and systematically for compliance with GMP and to assess the effectiveness of the quality assurance system. Those audits should cover all aspects of manufacture. The frequency and scope of audits should take into consideration the status and importance of the areas to be inspected, as well as the results of previous audits.

5.1.2.14 Internal audits should be conducted by staff who have been trained and are competent in internal audit procedures and should include, where practicable, staff who do not have direct responsibility for the processes being audited. Alternatively, independent external auditors may be used.

5.1.2.15 Where the need for corrective action has been identified, steps should be taken to address any observed deviations from the documented quality system and manufacturing procedures. Corrective and preventive action should be monitored for effectiveness and modified if necessary. Documented procedures should be amended if there is an identified need to do so.

5.1.2.16 Records should be kept of all internal audits undertaken, the outcomes of those audits, details of any corrective and preventive action taken and the effectiveness of such action.

5.1.2.17 product and processes are monitored and the results taken into account in batch release, in the investigation of deviations and, with a view to taking preventive action to avoid potential deviations occurring in the future;

5.1.2.18 arrangements are in place for the prospective evaluation and approval of planned changes and their approval prior to implementation taking into account regulatory notification and approval where required. After implementation of any change, an evaluation is undertaken to confirm that the quality objectives were achieved and that there was no unintended adverse impact on product quality;

5.1.2.19 regular reviews of the quality of veterinary products are conducted with the objective of verifying the consistency of the process and identifying where there is a need for improvement;

5.1.2.20 a state of control is established and maintained by developing and using effective monitoring and control systems for process performance and product quality;

5.1.2.21 continual improvement is facilitated through the implementation of quality improvements appropriate to the current level of process and product knowledge;

5.1.2.22 there is a system for Quality Risk Management (QRM);

5.1.2.23 deviations, suspected product defects and other problems are reported, investigated and recorded. An appropriate level of root cause analysis is applied during such investigations. The most likely root cause(s) should be identified and appropriate corrective actions and/or preventive actions (CAPAs) should be identified and taken. The effectiveness of CAPAs should be monitored.

The reader is referred to ICH Q10 and WHO TRS 986 for an elaborate explanation on each of the pharmaceutical quality system elements.

5.1.3 Quality control

A system of quality control should be in place to ensure that products comply with their required specifications and standards.

5.1.3.1 Quality control guidelines

General

All manufacturers should have an identifiable quality control function. This function should be under the authority of a person (with appropriate qualifications and experience), who has access to one or more control laboratories. Adequate resources must be available to ensure that all the quality control arrangements are effectively and reliably carried out. Where practicable, a quality control laboratory should be available and be adequately staffed and equipped for the performance of all quality control tests required before, during and after manufacture. Where there is no in-house facility, or the in-house facility does not have the capability of doing all required quality tests, satisfactory alternative arrangements for the required quality control testing should be made. The laboratory from which the outsourced activities are carried out should have been audited and periodic reviews should be done. The principal duties of the head of Quality have other duties, which may include:

i. establishing adequate quality control specifications for all materials at all stages of manufacture and for the finished product
ii. establishing, documenting, validating, and implementing all quality control test procedures
iii. assessing and releasing/rejecting starting and intermediate materials for each batch
iv. assessing and releasing/rejecting each batch of finished product for supply (e) keeping reference/retention samples of materials and products
v. ensuring the correct labelling of containers of materials and products
vi. monitoring the suitability of packaging materials
vii. monitoring the stability of the products, the suitability of expiry dates and product storage conditions.

5.1.3.2 Quality control Laboratory

Quality control laboratories should be separated from production areas. This is particularly important with laboratories that handle microorganisms. Quality control laboratories should be designed to suit the operations carried out in them. Space should be sufficient to avoid mix-ups and cross-contamination. There should be adequate storage for samples and records. Sensitive instruments should be protected from adverse effects such as vibration, electrical interference, and humidity.

5.1.3.3 Raw material testing

Conduct thorough testing of raw materials before use to ensure they meet specifications for purity, potency, and quality. Maintain records of all raw material testing results and certificates of analysis for traceability and documentation purposes.

5.1.3.4 In-process monitoring

Implement procedures for real-time monitoring of critical process parameters during manufacturing to detect deviations and ensure product quality.Conduct periodic sampling and testing of in-process materials to verify compliance with specifications and identify any potential issues early.

5.1.3.5 Finished Product Testing

Perform comprehensive testing of finished ectoparasiticide products to confirm identity, potency, purity, and stability. Retain samples of finished products for future reference and testing in case of complaints or regulatory enquiries.

5.1.3.6 Retention samples

Quality Control should take and retain samples of:

i. at least each batch of active starting material
ii. each batch of finished product.

Retention samples of materials and products should be of a size sufficient to permit at least a full re-examination. In the case of active raw materials, the quantity taken should be at least twice the quantity required to establish identity and purity. In the case of finished products, the number of units retained will depend on the product and should be adequate to permit re-examination at a suitable time and investigation of possible complaints.

Retention samples from each batch of finished products should be retained for at least 12 months after the expiry date of the products to which they relate or, if there is no expiry date, for at least 6 years after the date on which the manufacture of the products was completed. Where practicable, these samples should be kept in their final packaging. Where the finished product samples are not stored in their final packaging, the packaging chosen should be of the same materials as the manufactured product. Retention samples should be stored under the recommended conditions.

Samples of starting materials (other than solvents, gases, and water) should be retained for at least two years after the release of the product, if their stability allows. This period may be shortened if their shelf life, as mentioned in the relevant specification, is shorter.

5.1.3.7 Stability Monitoring

There should be an on-going stability monitoring programme in place for at least one batch of each ectoparasiticide product manufactured in a given year.

All Out of specification results to the stability program should be handled according to the Quality Management System and these should be reported to the Authority.

5.1.4 Personnel and Training

5.1.4.1 General

The manufacturer should have an adequate number of personnel with the necessary qualifications, training, and practical experience. Additionally, there should be documented on the job training following a training schedule that is developed in line with training needs. Specific qualifications for key personnel will be defined in the section below. The responsibilities placed on any one individual should not be so extensive as to present a risk to quality. The manufacturer should have an organisational chart showing the names of key personnel, as well as their areas of responsibility and lines of authority. People in responsible positions should have written job descriptions describing their specific duties. There should be no gaps or unexplained overlaps in the responsibilities of those personnel concerned with the application of GMP. People in responsible positions must have adequate authority to carry out their responsibilities. The duties of persons in responsible positions may be delegated to designated deputies with relevant qualifications and experience. Records should be kept of those delegations. Operators’ verbal and written communication skills should be sufficient for them to respond to training, accept and implement instructions exactly and, where their duties require it, fill out forms correctly.

5.1.4.2 Key personnel

All premises shall be licensed by the Authority in terms of section 55 (2) of the Medicines and Allied Substances Control Act; and under the overall supervision of a veterinary surgeon/ pharmacist licensed in terms of section 55 (3) of the Act read together with section 9 of the Medicines and Allied Substances Control (general) Regulations SI 150 of 1991. Key personnel include the persons nominated as responsible for Production and for Quality Control and, the Quality Assurance person (s) is responsible for product release. Normally, key positions should be occupied by full-time personnel. The person with overall responsibility for Production usually has responsibility to:

i. ensure that products are produced and stored according to documented procedures
ii. approve procedures relating to production operations and ensure their strict implementation
iii. approve and monitor any subcontracted production work
iv. ensure that production records are evaluated and signed by an authorised person before they are submitted for product release
v. ensure that production areas, premises and equipment are maintained to an appropriate standard
vi. ensure that appropriate validations are conducted

vii. ensure that initial and continuing training of production personnel are conducted, according to need.

The person with overall responsibility for Quality usually has responsibility to:

i. evaluate and authorise master manufacturing and packaging documents
ii. approve specifications, sampling instructions, test methods and other quality control procedures
iii. approve or reject raw materials, packaging materials, and intermediate, bulk and finished products
iv. review completed batch records as part of the release procedures (e) ensure that all necessary testing is carried out
v. approve and monitor any contract analysts
vi. monitor quality performance of subcontract manufacturers
vii. check the maintenance of the quality control area, premises, and equipment
viii. ensure that appropriate validations are conducted
ix. ensure that initial and continuing training of quality control personnel are conducted, according to need
x. approve and monitor the suppliers of materials.

5.1.4.3 Qualifications and experience

The persons responsible for Production and Quality should have a relevant degree or diploma in fields such as veterinary science, veterinary therapeutics, pharmacy, chemistry, or a related discipline a relevant scientific qualification at tertiary level and/or have had relevant practical experience and the necessary competencies in the manufacture of products in accordance with GMP requirements.

5.1.4.4 Training and competency assessment

i. Training should be provided for all personnel whose duties take them into production areas or into quality control laboratories, including technical, maintenance and cleaning personnel. Training should also be given to other personnel whose activities could affect product quality. Particular attention should be given to the training needs of casual employees.
ii. Training programs should be appropriate to the identified needs of staff and be approved by the head of either Production or of Quality, as appropriate. The effectiveness of the training program should be monitored.
iii. Training programs should include initial training in the basic principles of GMP, as well as training appropriate to the duties assigned to staff. Programs should also include ongoing training and refresher training, including training in changes to the manufacturing process and procedures. Training programs should specifically address the concept

of quality assurance, as well as relevant aspects of sanitation and personal hygiene.

iv. Records should be kept of all internal and external training programs and the various training activities undertaken by individual staff.

v. Staff should be assessed for their competence to perform the duties assigned to them. Records should be kept of those assessments.

vi. Personnel working in areas where contamination is a hazard (e.g. cleanrooms or areas where highly active, toxic, infectious or sensitising materials are handled) should be given specific training in those aspects of manufacture.

vii. Personnel should have a clear understanding of their responsibilities.

viii. Personnel should not be required, or allowed, to sign or initial a document unless they have been trained and assessed as competent in the work practices associated with the signature and in the significance of the signature.

ix. A register of staff signatures and initials should be maintained. Entries should be updated at regular stated intervals and the previous records archived.

x. Visitors or untrained personnel preferably should not be taken into active production and quality control areas. If access is unavoidable, they should be adequately supervised and be given information in advance, particularly about personal hygiene and prescribed protective clothing.

5.1.5 Premises

Premises should be licensed with the Medicines Control Authority of Zimbabwe in line with the Medicines Control Act and Regulations. Inspections will be done on initial licensing, annually for the first three years, then once every three to five years using a risk based approach. As a general rule, ectoparasiticides should not be manufactured in the same area as other veterinary medicinal 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, provided that 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 plant, using equipment dedicated to ectoparasiticides manufacture. Special measures are needed to prevent cross-contamination with agricultural chemicals, particularly where shared facilities, such as packing rooms, are used. 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. An HVAC system is not mandatory, however, there should be an effective environmental monitoring/ control program which includes temperature mapping, temperature control and temperature and humidity monitoring.

5.1.6 Waste Management

Proper disposal of waste generated during the manufacturing process is essential. This includes managing chemical, biological and physical waste in accordance with local regulations to prevent environmental contamination.

5.1.7 Compliance with Regulations

Manufacturers must comply with relevant environmental regulations and guidelines set forth by regulatory authorities in the regions where they operate.

5.1.8 Cleaning and sanitation

Processing areas, laboratories and storage areas should be kept in a clean, sanitary, and orderly condition. Documented cleaning procedures should be available for all areas. These should describe:

i. the areas to be cleaned, the frequency of cleaning, and specific requirements of individual areas
ii. the materials, concentrations, and equipment to be used
iii. the methods used to decontaminate cleaning equipment.

Where the removal of traces of product is critical, evidence to demonstrate that the cleaning process is effective should be available. In these cases, unless standards of cleanliness are prescribed by a regulatory authority, manufacturers should determine appropriate limits based on assessed risk. The premises should be kept free of insects, birds, rodents, and other animals, either by containment or by appropriate control measures. A documented pest control program should be in place, which should be monitored for effectiveness. Records should describe the location of bait stations, materials used, monitoring frequency and effectiveness.

5.1.9 Storage areas (including receipt and dispatch)

i. Storage areas should be organised and be of sufficient area to permit the effective separation and identification of the various materials and products stored in them. Materials or products that are rejected, returned, or recalled should be segregated and secured.
ii. Storage areas should provide storage conditions appropriate to the materials and products held in them. They should be clean, dry, and maintained within acceptable temperature limits. Where special storage conditions are required (e.g., temperature and humidity) these should be provided and monitored. However, these requirements do not preclude outdoor storage of materials where outdoor storage does not adversely affect quality.
iii. Receiving and despatch bays should protect materials and products from the weather and should be designed and equipped to allow containers of incoming materials to be cleaned, where necessary, before storage.
iv. On receipt, all starting materials (including labels, printed cartons and other packaging material) should be subject to effective quarantine and release control.
v. Where quarantine status is ensured by storage in separate areas, these areas should be clearly marked. Any system replacing a physical quarantine

system (such as a computerised access system) should provide at least an equivalent level of security.

vi. Sampling of raw materials should be conducted in such a way that contamination of the material, or cross-contamination of other materials, is prevented. There should be a separate sampling area for highly active, hazardous, or toxic raw materials.

vii. Highly active, hazardous, or toxic materials or products, or otherwise incompatible materials should be stored in such a way as to not pose a risk to other materials or products.

viii. Labels should be stored in segregated areas with restricted access. Other pre-printed packaging materials should be stored in such a way as to prevent mix-up.

5.1.10 Production areas

i. The operations carried out in any area should be compatible so that the integrity of any product made in the area is not threatened.

ii. Premises should be laid out in a way that allows the orderly and logical positioning of equipment and materials so as to minimise the risk of confusion between different ectoparasiticides or their components, to avoid cross-contamination and to minimise the risk of omission or wrong application of any of the manufacturing or control steps.

iii. Joins between walls and floors should be easy to clean, adequately sealed and where appropriate, coved to form a smooth curve between the floor and wall.

iv. Wherever possible, wood or wood-based material should be avoided as a material of construction or support for equipment or materials in production areas, especially where it may be wetted. If used, it should be sealed with a coating that is resistant to chipping, disinfectants and cleaning agents and that is easily cleaned.

v. The use of wood-based pallets should be only be used if they are heat treated, otherwise be avoided in production areas where there is a risk of contamination of the product.

vi. Pipe work, light fittings, ventilation points and other services should be designed and located to avoid the creation of recesses that are difficult to clean. As far as practicable, they should be accessible from outside the manufacturing areas for maintenance purposes.

vii. Production areas should be effectively ventilated and allow, where necessary, control of air flow, temperature, humidity, and filtration appropriate to the products handled, the operation undertaken and the external environment.

viii. The arrangements for weighing or measuring raw materials should minimise cross-contamination. This may require the use of separate weighing or dispensing rooms designed and reserved for that use. Dispensing rooms should not be used as storage areas for starting and other materials.

ix. Where dust is generated (e.g., during sampling, weighing, mixing and processing operations, or packaging of dry products), specific provision should be made and precautions taken, to avoid cross-contamination (e.g. efficient dust extraction, use of dedicated enclosed areas) and to facilitate cleaning.
x. Materials likely to shed fibres or other contaminants, such as wooden pallets or fibreboard, should not be taken into areas where products or clean containers are exposed.
xi. Production areas should be well lit, particularly where visual on-line controls are carried out.

5.1.11 Ancillary areas

i. Staff amenities, including lunch rooms, should be separate from storage, production and quality control areas.
ii. Clean and well-ventilated toilets and changing rooms should be provided. These should be easily accessible and suitably isolated from any production, quality control or storage areas. They should be appropriate for the number of users and should be maintained in a tidy and hygienic manner, with an adequate supply of hot and cold water, soap, and hygienic hand-drying facilities.
iii. A sufficient number of clean hand basins, with a satisfactory supply of hot and cold water, soap or detergent dispensers, and hygienic hand-drying facilities should be provided near working areas for use by production personnel.
iv. Maintenance workshops should, as far as possible, be separate from production areas. Whenever parts or tools are stored in the production area, they should be kept in rooms or lockers reserved for that use.

5.1.12 Animal houses

Areas in which animals are housed should be adequately isolated from storage and processing areas, with separate access for animals and separate air handling facilities.

5.1.13 Equipment

5.1.13.1 Manufacturing principles

Equipment used in the manufacture of ectoparasiticides must be suitable for its intended purpose and appropriately operated, maintained and cleaned. Equipment must be correctly installed and operated in accordance with written instructions that are appropriate for the equipment. The design and layout of equipment must be such that:

i. the risk of manufacturing error is minimised,

ii. effective cleaning and maintenance are possible, in order to avoid cross-contamination of either intermediate materials or the finished product, the buildup of dust or dirt and, in general, to avoid any adverse environmental effect on the quality of the product.

5.1.13.2 Equipment guidelines

General

i. Equipment used for the manufacture (including testing) of ectoparasiticides should be designed, located, and maintained to suit its intended purpose and should be installed and positioned in such a way as to minimise any risk of error or cross-contamination.
ii. Equipment should be used in accordance with written instructions that are appropriate to the equipment and consistent with any operating instructions issued by the equipment manufacturer.
iii. Production equipment should not present any hazard to the manufactured products (e.g., by contamination of processed materials or finished products, or their containers, with lubricants or other extraneous substances). The parts of the production equipment that come into contact with materials being processed or the finished product must not be reactive, additive, or absorptive to such an extent that product quality is adversely affected.
iv. Equipment should be uniquely identified. This identification should be traceable to all records pertaining to the equipment.
v. If prone to failure or variance, equipment used for critical steps in the manufacturing process should be monitored by devices capable of recording the necessary operating parameters or should be equipped with alarm devices to indicate malfunction. If such devices are not practical, the output should be monitored to ensure early detection of variance.
vi. Balances and other measuring equipment required for production and quality control operations should be available and should have an appropriate range and degree of precision. Equipment should be properly positioned before use.
vii. Fixed pipework should be clearly labelled to indicate the contents and, where applicable, the direction of flow. Pipes should be adequately sloped for drainage and constructed without ‘dead-legs’. There should be measures in place to ensure that materials transferred via pipelines are delivered to the correct destination.
viii. Defective equipment should, if possible, be removed from production and quality control areas, or be clearly labelled as defective.

5.1.13.3 Equipment qualification and validation

Newly installed equipment that is critical to the manufacturing process should be formally commissioned. There should be protocols for installation qualification (IQ) and operation qualification (OQ) of equipment. These should include the development and implementation of procedures for operation, calibration, maintenance, and cleaning.

Equipment that has been taken out of service, modified, or undergone major repairs should be formally approved for re-entry into service.

5.1.13.4 Maintenance

All equipment should be properly maintained, and records of this maintenance should be kept. In addition, equipment should be inspected for serviceability before any operation begins. Repair and maintenance operations should not present any hazard to product quality. Where continued maintenance of specific equipment is essential to product quality, documented maintenance procedures and records should include the following:

i. details and frequency of preventive maintenance requirements
ii. action to be taken if equipment maintenance requirements cannot be met
iii. records of preventive maintenance, including the name of the service-person, any deviation from the procedure and a statement or authorising signature documenting the condition of the equipment following the service.

5.1.13.5 Calibration

Each item of equipment used in manufacture or for quality control purposes that measures or depends on a physical parameter (e.g., measuring, weighing, recording and control equipment), should be calibrated at defined intervals, in accordance with a written procedure. That procedure should describe the method and frequency of calibration or observation, taking into account any statutory requirements, as well as the action to be taken when results deviate from defined acceptance limits.

Where appropriate, verification checks should be performed at a frequency consistent with the use of the equipment, in accordance with a written procedure. Records should be kept of any calibrations, verification checks or observations carried out on such equipment. Those records should contain sufficient information to show that the required calibrations/observations have been carried out and provide details of any necessary corrective action taken.

Records of any equipment calibration should show the actual results observed and the acceptance criteria. Where practicable, each item requiring calibration should bear a label or tag indicating that calibration has been carried out and when the next calibration is due. Alternatively, a computer-based maintenance system that flags the need for calibration can be accepted, provided that it can be shown to be working effectively. There should be evidence to demonstrate that the particular calibrating devices used are themselves accurate. Contractors who calibrate equipment should be certified by a certification agency.

5.1.13.6 Cleaning

Manufacturing equipment should be designed so that it can be easily and thoroughly cleaned. Where necessary, it should be easily dismantled for cleaning. It should be cleaned according to detailed written procedures, and only stored in a clean, dry environment. Records should be kept of equipment cleaning operations.

To facilitate cleaning, equipment should be mobile or clear of walls and floors. Where this is not practical, equipment should be sealed to the surfaces it touches. Permanently fixed product and process-water pipelines should have sanitary couplings and be sloped for drainage. Washing and cleaning equipment should be chosen and used in such a way that it is not a source of contamination.

Pipes for distilled, purified and, where appropriate, other water should be sanitised according to written procedures that detail the action limits for microbiological contamination and the measures to be taken if action limits are exceeded. Equipment should be cleaned to the frequency and extent necessary to preserve product integrity. A cleaning record should be kept either on the batch record or in an equipment logbook.

Validation of cleaning procedures should be considered where traces of ingredient may pose significant contamination or toxicity risk in following product batches.

5.1.14 Documentation

5.1.14.1 Manufacturing principles

Manufacturers of ectoparasiticides must establish and maintain a system of documentation, document control and record keeping that:

i. provides precise specifications for starting materials, intermediate materials and finished products, manufacturing formulae and instructions, and operating procedures for associated manufacturing and quality control activities,
ii. provides a complete history of each item, batch, or quantity manufactured in a specified timeframe, of ectoparasiticide produced at the premises,
iii. establishes a traceable connection between raw materials and the finished product.

5.1.14.2 Documentation guidelines

General

All processes and associated activities in the manufacture of ectoparasiticides should be documented and the documents subjected to a system of document control. Documents should be approved, signed, and dated by appropriate and authorised persons. In the case of master manufacturing formulae, manufacturing instructions, and packaging and labelling instructions, a second authorised person should check, reconcile, endorse, and date both the formula and instructions.

Issue of working documents and forms should be limited to photocopying from current, authorised, signed, hard master documents or printing from access-controlled authorised electronic versions.

Documents should be legible, readily identifiable, and retrievable. They should not include superfluous data and, at the working level, should be written in the imperative (i.e., as instructions rather than statements of what is desired). They should be laid out in an orderly fashion and be easy to check. Documents should not be handwritten. Data entries may be handwritten or machine-printed, and must be clear, legible, and permanent. Sufficient space should be provided for such entries.

The contents of documents should be unambiguous. The title, nature and purpose should be clearly stated. The document should clearly identify the way in which it is to be used, and by whom it is to be used. It should include, or be identifiable to, the issuing premises and should also include the following information:

i. a unique number identifying the document
ii. the version number and date it became effective
iii. the page number of the total number of pages of the document on each page
iv. provision for authorisation.

Relevant documentation should be available to cover manufacturing and associated activities at all locations. Reproduced documents should be clear and legible. The reproduction of working documents from master documents (e.g., by photocopying or by computer printout), should not allow error to be introduced through the reproduction process. A designated competent person should initial each reproduced document before issue to signify that it is complete, legible, and appropriate.

Any correction to a document should permit the reading of the original information. Corrections should be handwritten clearly and legibly in permanent ink, and initialled and dated by an authorised person. Where appropriate, the reason for the alteration should be recorded. Where appropriate, new, or revised documents should be introduced following a formal commissioning and training period.

5.1.14.3 Document control

The system of document control should be documented. That document should define the procedures in place for:

i. approval and regular review of documented procedures
ii. distribution of documents
iii. removal of obsolete documents from all points of issue and use
iv. prevention of inadvertent use of superseded documents.

5.1.14.4 Batch Records

i. Maintain detailed batch records documenting all aspects of the manufacturing process, including equipment used, personnel involved, in-process controls, and testing results.
ii. Ensure batch records are accurate, complete, and reviewed by authorized personnel before final approval and release of the product.

5.1.14.5 Standard Operating Procedure (SOPs)

i. Develop and maintain up-to-date SOPs for all manufacturing processes, equipment operation, cleaning procedures, and quality control testing.
ii. Ensure SOPs are readily accessible to all personnel and followed consistently to maintain compliance with GMP requirements.

5.1.14.6 Change Control and Deviation Management

i. Implement a formal change control process to evaluate and approve any proposed changes to manufacturing processes, equipment, or procedures.
ii. Document and investigate any deviations from established procedures and implement corrective and preventive actions as necessary to prevent recurrence.

6.0 REFERENCES

6.1 Australian Pesticides and Veterinary Medicines Authority (APVMA) - Australian code of good manufacturing practice for veterinary chemical products, 2007, Annex 5

6.2 Australian Code of Good Manufacturing Practice for Veterinary Chemical Products

6.3 Medicines and Allied Substances Control Act 15:03

6.4 WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eight Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2 http://www.who.int/medicines/publications/pharmprep/en/index.html

6.5 MCAZ Good Manufacturing Practice Guideline, **MCAZ/LED/GL 09**.

7.0 HISTORY

DOCUMENT HISTORY		
Revision Number	Date Approved	Date Reviewed: …………………………..

		Reason for Change and Amendments ………………………………………….. The following changes/amendments were done from Revision … to Revision ….