GUIDELINE ON GOOD MANUFACTURING PRACTICE (GMP) FOR VETERINARY PREMIXES

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Introduction

The implementation of the Regulations on veterinary medicinal products regulated under Drug Control Authority (DCA) shall be on all products containing scheduled poison(s) as defined in the Poisons Act 1952, non-poison (OTC) and products containing pesticides for internal use / external use (control of endoparasite) including veterinary premixes intended to be administered to animals for **medicinal purpose.** As a consequence, they must be manufactured in compliance with GMP standards.

Regardless of the size and nature of the manufacturing premises, all manufacturers of veterinary products, unless exempt, are required to comply with GMP requirements taking into account the type of product being manufactured and its intended use. 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.

A separate guide on GMP for the manufacture of veterinary medicinal products is available. Please refer to PIC/S Guide to Good Manufacturing Practice for Medicinal Products. This guideline is established particularly to provide guidance on good manufacturing practices for the manufacture of veterinary premixes.

Veterinary premixes are defined as mixtures of one or more active ingredients, usually in suitable bases, which containing scheduled poisons (substances listed in First Schedule of the Poison Act 1952) or non-poisons substances that are used exclusively in the preparation of animal feed for medicinal purpose. Premixes occur in granulated, powdered, semi-solid or liquid form and may also occur in pelleted form.

Quality Management

1. Veterinary premixes 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 premixes must be manufactured in such a way that they comply with their registered particulars and that there is batch-to-batch consistency.

2. The attainment of these quality objectives is the responsibility of senior management and requires the participation and commitment of all staff, at all levels within the manufacturing organization. In order 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).

Quality Assurance (QA)

3. **Quality Assurance (QA)** is a wide-ranging concept covering all aspects of the manufacturing process that individually or collectively influences the quality of a manufactured product. It is the sum total of the organised arrangements made to ensure that veterinary premixes are consistently manufactured in an appropriate manner to the quality standards required for their intended use. Quality Assurance therefore incorporates GMP and Quality Control as well as other factors outside the scope of this Guideline such as environmental and occupational safety controls.

4. Quality Assurance requires manufacturers to have in place a quality management system.

   - It encompassing organizational structure, responsibilities, procedures, instructions, processes and resources necessary for implementing quality management.

   - That system must ensure that facilities and equipment are suitable for the types of products manufactured, that there are sufficient competent personnel and that appropriate procedures are in place to ensure appropriate quality standards are met.

   - The system must ensure that all materials involved in the manufacturing process (including raw materials, intermediate materials or samples from any material relevant to product quality) are

checked and tested, where necessary to ensure that they meet required quality standards before they are released for use.

- Procedures must be in place to ensure that the finished product has been manufactured correctly and meets all the required quality tests before it is released for supply or sale.

5. The Quality Management System must be relevant to the needs of the product. It must be fully documented, monitored for effectiveness and incorporate an element of continuous improvement.

Good Manufacturing Practice (GMP)

6. **Good Manufacturing Practice (GMP)** is that part of Quality Assurance which ensures that products are consistently manufactured to the quality standards appropriate for their intended 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.

7. The basic requirements of GMP are that :

a) all manufacturing processes are clearly defined, are systematically reviewed in the light of experience, and shown to be capable of consistently manufacturing veterinary products that comply with their specifications and the required quality standards;

b) critical steps of manufacturing processes and significant changes to the processes are validated;

c) all necessary facilities for GMP are provided, including :

(i) appropriately qualified, trained and / or experienced personnel
(ii) adequate premises and space
(iii) suitable equipment and services
(iv) correct materials, containers and labels
(v) approved procedures and instructions
(vi) suitable storage and transport

d) instructions and procedures are written in an instructional form in clear and unambiguous language, specifically applicable to the facilities provided;

e) operators are trained to carry out procedures correctly;

f) records are made manually and / or by recording instruments during manufacture which demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the product was as expected. Any significant deviations are fully recorded and investigated;

g) records of manufacture including distribution, that enable the complete history of a batch to be traced are retained in a comprehensible and accessible form;

h) a system is available to recall any batch of product from sale or supply;

i) complaints about marketed products are examined, the causes of quality defects investigated and appropriate corrective and preventive measures are taken in respect of the defective products and to prevent re-occurrence.

Quality Control (QC)

8. **Quality Control (QC)** is that part of GMP which is concerned with specifications, sampling and testing, and with the organization, documentation and release procedures which 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.

Process Control and Change Control

9. All critical steps in the manufacturing process, and any changes to these steps, should be documented. Manufacturing processes should be reviewed at defined regular intervals and the outcome of that review documented and acted upon.

10. A change control system should be in place to manage significant manufacturing and product quality changes. This should include application to the competent authority, to vary product details where necessary.

Personnel

11. There should be sufficient personnel possessing the skills and qualifications necessary for the manufacture of veterinary premixes. An organization chart setting out the qualifications and responsibilities of the supervisory staff must be drawn up.

12. All personnel must be informed clearly in writing of their duties, responsibilities and powers, especially when any change is made, in such a way as to obtain the desired product quality.

13. Key personnel include the persons nominated as responsible for Production and for Quality Control should be occupied by full-time personnel and be independent from each other. An authorized person should be totally responsible for the release or rejection of the veterinary product.

14. The persons responsible for Production and for Quality Control should have a relevant scientific qualification and / or have had relevant practical experience and the necessary competencies in the manufacture of veterinary premixes in accordance with GMP requirements.

15. 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.

16. Personnel must be trained both in GMP generally and their specific duties. Continuing training should also be given and its effectiveness should be periodically assessed. Training programs should be appropriate to the identified needs of personnel and be approved by the head of either Production or of Quality Control, as appropriate. Training records should be kept.

17. 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.

18. Detailed hygiene programs include procedures relating to the health, hygiene practices and clothing of personnel should be established. All personnel where relevant, should receive medical examination upon recruitment to ensure that their health status does not pose a risk to product quality and that they are able to carry out required tasks (e.g. visual checks of labels or containers). After the first medical examination, examinations should be carried out when necessary for the work and personal health.

19. Steps should be taken to ensure as far as is practicable that no person affected by an infectious disease or having open lesions on the exposed surface of the body is engaged in the manufacturing activities.

20. Every person entering the manufacturing or quality control areas should wear protective garments appropriate to the operations carried out there. Suitable clothing to protect the personnel and / or product, including where appropriate, hair coverings, gloves, masks, and footwear should be worn by all personnel in processing and packaging areas over or in place of normal clothing. Protective clothing must be cleaned and / or replaced at regular intervals.

21. Direct contact should be avoided between the personnel's hands and the exposed product as well as with any part of the equipment that comes into contact with the products.

22. Eating, drinking, chewing or smoking, or the storage of food, drink, smoking materials or personal medication in the production and storage areas should be prohibited. In general, any unhygienic practice within the manufacturing areas or in any other area where the product might be adversely affected should be forbidden.

Premises

23. Premises should be situated in an environment which, when considered together with measures to protect the manufacture, presents minimal risk of causing contamination of materials or products.

24. Lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the veterinary premixes during their manufacture and storage, or the accurate functioning of equipment.

25. Premises should be designed and equipped so as to afford maximum protection against the entry of insects or other animals.

26. Steps should be taken in order to prevent the entry of unauthorized personnel or materials. Production, storage and quality control areas should not be used as a right of way by personnel who do not work in them, or for the transport of materials not being currently used in them. They should not be used as storage areas for obsolete materials or equipment.

27. Manufacturing facilities used to manufacture veterinary premixes under the scope of this guideline should not be used for the manufacture of other veterinary medicinal products.

28. Work areas and equipment used for the production or storage of veterinary premixes under the scope of this guideline thereof should not be used for, and should be physically separated from work areas and equipment used for the manufacture and storage of fertilizers, herbicides, insecticides, fungicides, rodenticides and other pesticides unless such articles are approved for use in the manufacture of veterinary premixes.

29. Documented cleaning procedures should be available for all areas. These should describe :

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

Manufacturing Area

30. Premises should preferably be laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.

31. Where starting and primary packaging materials, intermediate or bulk products are exposed to the environment, interior surfaces (walls, floors and ceilings) should be smooth, non-porous, free from cracks and open joints, should not shed particulate matter and should permit easy and effective cleaning, if necessary, disinfection.

32. Wood or wood-based material should be avoided as a material of construction or support for equipment or materials in production areas. The use of wood-based pallets should be avoided in production areas where there is a risk of contamination of the product.

33. Floor drains should generally be avoided, as they are a potential source of contamination. Where they are necessary, they should be of adequate size, flush with the floor, screened and have trapped gullies. Drains should generally be underground. Open channels should be avoided where possible, but if necessary, they should be shallow to facilitate cleaning and disinfection.

34. Manufacturing premises should provide adequate space, well lighted and ventilated for the proper performance of the following operations :

- the receipt, control and storage of materials
- manufacturing of veterinary premixes
- packaging and labelling
- routine maintenance of equipment

35. Ventilation within the manufacturing premises should provide sufficient air exchange to prevent unacceptable accumulation of dust and to remove contaminated air.

36. Because of the large amount of dust generated during the manufacture of bulk material of veterinary premixes, specific attention should be given to the need to avoid cross-contamination either by :

- physical separation from other aspects of manufacture,
- installation of closed / sealed transport systems,
- providing appropriate and effective air-locks, air / dust extraction and hygiene,
- using cleaning and decontamination procedures of known effectiveness, as ineffective cleaning of equipment is a common source of cross-contamination.

However, installation of such sealed transport systems does not eliminate the need for regular cleaning of production areas.

37. Cleaning programs should specifically address the build up of dust, sticky and corrosive materials and also in the issue of spilt products or raw materials. Dry cleaning of spillages is preferable compared to wet.

38. The manufacture of veterinary premixes often requires the use of large quantities of vegetable matter, which is likely to attract insects, birds, rodents and other pests. Premises should be designed, equipped and operated to minimize the risk and should also be subject to a regular pest control program.

39. External driveways and paths surrounding the manufacturing area should be sealed to prevent the tracking of dirt and mud on the wheels of forklifts and other mobile equipment into the production areas.

40. An efficient waste disposal system should be in place to regularly remove waste or contaminated materials from the manufacturing premises. Disposal of waste materials should be done in accordance with the requirements outlined by the relevant authorities. Written procedures should be established by the manufacturer and appropriate records should be kept.

41. Water used in the manufacture of veterinary premixes should be of suitable quality for animals. The conduits for water should be of an inert nature. The quality of water required should be specified and be consistent with approved registration details.

Storage Areas

42. Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products: raw material, packaging materials and finished products, products in quarantine, released, rejected, returned or recalled.

43. Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean, tidy and dry and maintained within acceptable temperature limits. Where special

storage conditions are required (e.g. temperature, humidity) these should be provided, checked and monitored.

44. All storage areas should be maintained in a manner which minimizes the risk of product contamination by vermin and birds.

45. Storage areas should be laid out to permit rotation of stocks, preferably on a 'First In First Out' (FIFO) or 'First Expiry First Out' (FEFO) system.

46. Receiving and dispatch bays should protect materials and products from the weather. Receptions areas should be designed and equipped to allow containers of incoming materials to be cleaned where necessary before storage.

47. To ensure proper identification of all stored raw materials, all fixed or mobile bins, silos, tanks and bagged containing materials should be clearly identified by either labelling or numbering. Documentation and records should be maintained.

48. Special and segregated areas should be available for storage of flammable and explosive substance, highly active materials or products and rejected, recalled or returned materials / products. They should be stored in safe and secure manner.

49. The need to store on-site, potentially hazardous materials or materials that may be mistaken for veterinary premixes ingredients should be minimised to the extent that this is practical. Materials such as pest control baits, boiler water treatments, cleaning agents or substances used to control odour should be stored securely away from the storage of the starting materials and access point to the production line. These materials should be stored close to the point of intended use.

50. There should normally be a separate sampling area for starting materials. If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross-contamination.

51. 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.

Quality Control Areas

52. A quality control facility should be available and separated from production areas, adequately staffed and equipped for the performance of all quality control tests required before, during and after manufacture. When the in-house facility does not have the capability of doing all required quality tests, satisfactory alternative arrangements for the necessary quality control testing should be made.

53. Quality Control laboratories should be designed to suit the operations to be carried out in them. Sufficient space should be given to avoid mix-ups and cross-contamination. There should be adequate suitable storage space for samples and records.

54. Separate rooms may be necessary to protect sensitive instruments from vibration, electrical interference, humidity, etc.

Ancillary Areas

55. Rest and refreshment rooms should be separate from other areas.

56. Facilities for changing clothes, wash-up and toilet purposes should be easily accessible and appropriate for the number of users. Toilets should not directly communicate with production or storage areas.

57. Rest, change, wash-up and toilet facilities should be well ventilated and of a type that permits good sanitary practices.

58. Maintenance workshops should as far as possible being separated from production areas. Whenever parts and tools are stored in the production area, they should be kept in rooms or lockers reserved for that use.

Equipment

59. Manufacturing equipment should be designed, located and maintained to suit its intended purpose. Repair and maintenance operations should not present any hazard to the quality of the products.

60. Manufacturing equipment should be designed so that it can be easily and thoroughly cleaned. It should be cleaned according to detailed and written procedures and stored only in a clean and dry condition.

61. 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.

62. Manufacturing equipment should not present any hazard to the products. The parts of the production equipment that come into contact with the product must not be reactive, additive or absorptive to such an extent that it will affect the quality of the product and thus present any hazard.

63. Equipment and machinery should have appropriate dust extraction and guarding system.

64. Equipment should be uniquely identified. This identification should be traceable to all records pertaining to the equipment.

65. Equipment which to be used for mixing and / or manufacturing operations should undergo appropriate and regular checks, at least once a year in accordance with written procedures pre-established by the manufacturer.

- All scales and metering devices used in the manufacture of veterinary premixes should be appropriate for the range of weights or volumes to be measured and shall be tested for accuracy regularly. All records must be kept.

- All mixers used in the manufacture of veterinary premixes should be appropriate for the range of weights or volumes being mixed and should be capable of manufacturing suitable homogeneous mixtures. Production personnel should be able to demonstrate the effectiveness of mixers with regards to homogeneity.

66. 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.

67. 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.

68. Equipment which coming into contact with veterinary premixes should be dried following any wet cleaning process.

69. Adequate clean out procedures for all equipment used in the manufacture and distribution of veterinary premixes are essential to maintain proper product potency and avoid unsafe contamination risk. Such procedures may consist of cleaning by physical means e.g. vacuuming, sweeping, washing, etc. Alternatively, flushing, sequencing of production or other equally effective techniques may be used.

- If flushing is utilized, the flushing material should be properly identified, stored and used in a manner to prevent unsafe contamination of other material.

- If sequential production of veterinary premixes is utilized, it should be on a pre-determined basis designed to prevent unsafe contamination of products residual.

70. Defective equipment should, if possible, be removed from production and quality control areas, or be clearly labelled as defective.

Documentation

71. Manufacturers of veterinary premixes must establish and maintain a system of documentation, document control and record keeping that :

- provide precise specifications for starting materials, intermediates and finished products, manufacturing formula and instructions, and operating procedures for associated manufacturing and quality control activities;

- provides a complete history of each item, batch or quantity manufactured in a specified time frame, of veterinary premixes produced at the premises;

- establishes a traceable connection between starting materials and the finished product.

72. Manufacturing documentations should be designed, prepared, reviewed and distributed with care; and should be approved, signed and dated by appropriate and authorized persons.

73. Documents should have unambiguous contents. Documents should be regularly reviewed and kept up-to-date. When a document has been revised, systems should be operated to prevent inadvertent use of superseded documents.

74. 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.

75. Documents should not be hand-written; although, where documents require the entry of data, these entries may be made in clear, legible, indelible handwriting. Sufficient space should be provided for such entries.

76. Any alteration made to the entry on a document should be signed and dated; the alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.

77. A documented procedure should be in place that defines the controls needed for the storage, protection, retrieval, retention time and disposal of records.

78. The records should be made or completed at the time each action is taken and in such a way that all significant activities concerning the manufacture of veterinary premixes are traceable.

79. Data may be recorded by electronic data processing systems, photographic or other reliable means, but detailed procedures relating to the system in use should be available and the accuracy of the records should be checked.

80. If documentation is handled by electronic data processing methods, only authorized persons should be able to enter or modify data in the computer and there should be a record of changes and deletions. Access should be restricted by passwords or other means.

81. Batch records that are stored electronically should be backed up by suitable means on a regular basis. It is particularly important that the data are readily available throughout the period of retention. Consideration should be given to storage of batch records and other critical records in a safe and secure environment.

82. Starting materials (raw materials and packaging materials) and finished products must be subject to written specifications which are compatible with data submitted for product registration.

83. Where specifications for raw materials are based on a valid Certificate of Analysis (CoA) provided by a supplier, a copy of that Certificate of Analysis should be suitably identified and authorized by an appropriate person and retained as part of the manufacturer's specifications.

84. Where water is treated for use as an ingredient, a specification for this process water should be developed, based on sound physical, chemical and microbiological principles.

85. There should be written procedures and records for the receipt of each delivery of each starting materials.

86. A written master formula should be established by authorized personnel and kept on a master file with a record of the dates of use. Manufacturing formulas can be issued to production personnel and implemented either manually or via a computerized batching system. No amendments may be made to a formula once it is issued to production unless made by authorized personnel and fully documented.

87. Each batch or production run of veterinary premixes should be identified with its own individual batch or production run number, code, date or other suitable identification applied to the label, package, and invoice or shipping document. This identification should permit the tracing of the complete and accurate manufacturing history of the product by the manufacturer.

88. All records pertaining to the manufacturing of veterinary premixes which identifying information such as the formulation, date of mixing, date of shipment, etc. including production batch records, starting materials source and its storage details, product quality test results and relevant verification results for flushing and sequencing should be kept. This information should be maintained for at least one year after the expiry date of the finished product batch for future reference e.g. customer complaints and recall.

89. In addition to the information which is part of the batch record, other original data such as laboratory notebooks and / or records should be retained and readily available.

90. Distribution records should be established to permit the manufacturer to relate complaints to specific product batches and / or production runs of veterinary premixes. This information may be helpful in instituting a recall.

91. The distribution records should be retained on the premises for not less than one year after the date of shipment of the veterinary premixes.

Production

Starting Materials

92. A documented raw material sourcing and purchasing program must be implemented that minimizes potential product quality and safety risks.

93. Relevant specifications for all materials used should be established and accessible at the site.

94. Starting materials should be sourced / purchased from suppliers who can demonstrate compliance with a quality assurance system and / or can demonstrate that their products comply with the purchase specifications.

95. All incoming raw materials and packaging materials should be checked to ensure that the consignment corresponds with the order. All raw materials received should be clearly labelled by the supplier with material name, weight, date of manufacture and / or expiry date, batch number, etc. Containers should be cleaned, where necessary.

96. Incoming shipments of materials shall be visually examined for identity and damage. Materials which have been subjected to conditions which may have adversely affected their identity, strength, quality or purity should not be accepted.

97. Only starting materials which have passed quality assessment and have been released by the Quality Control Department; and which within their shelf-life should be used.

98. Starting materials which found to be out of specification should be clearly identified and either returned to the supplier or not received until appropriately dealt with by authorized personnel.

99. Incoming raw materials and finished products should be physically or administratively quarantined immediately after receipt or processing until they have been released for use or distribution.

100. All materials and products should be stored under conditions that will minimize deterioration and should be stored in an orderly fashion to permit batch segregation and stock rotation.

101. Labels should be received, handled and stored in a manner that prevents label mix-ups and assures that the correct labels are used for the product. All deliveries of products whether bagged or in bulk should be adequately labelled to assure that the product can be properly used.

102. Labels and other pre-printed packaging materials including “approved” status labels should be stored in a secure manner that will permit issue only to authorized persons in accordance with documented procedures.

103. Manufacturing area should be thoroughly checked to ensure that no labels or packaging materials from the previous batch remain. Two or more products should not be labelled and packed in close proximity unless some form of physical barrier is provided or the distance is great enough to avoid a mix-up.

104. All labels and packaging materials should be checked annually. All outdated or obsolete materials must be destroyed as soon as practicable.

Process Control

105. Raw materials should be dispensed only by designated personnel, following a written procedure, in order to ensure that the correct materials are accurately weighed or measured into clean and properly labelled containers.

106. The dispensing operation should be supervised or verified to the extent necessary to ensure the accuracy of the weight / volume and the identity of the materials and all checks should be recorded.

107. Materials dispensed for each batch should be kept together, isolated from other materials and be conspicuously labelled with the product batch number.

108. Before any processing operation is started, steps should be taken to ensure line clearance so that the work area and equipment are clean, suitable for use and free from any raw materials, products, product residues or documents not required for the current operation.

109. The veterinary premixes must be manufactured in full accordance with authorized batch manufacturing instructions. Any variation from those instructions should be authorized in writing by an authorized person.

110. Delays in completion of the manufacturing process should be kept to a minimum. The maximum holding time for intermediate and bulk materials should be clearly defined and justified.

111. The different stages of production should be carried out according to written procedures which define, check and control the critical points in the manufacturing process. Records should be kept which confirm that procedures are followed and / or identify any deviation from them. Procedures should be subject to regular, critical appraisal to ensure that they continue to be effective.

112. Checks should be made to ensure that any electronic code readers, label counters or similar devices are operating correctly.

113. Veterinary premixes that have been involved in an unusual event (e.g. a mid-process breakdown in production or storage conditions) should only be reintroduced into the process after special inspection, investigation and approval by authorized personnel. Detailed records should be kept of this operation.

114. All intermediate yields and the final product yield should be checked and quantities reconciled against the theoretical or expected values by the authorized personnel. Any discrepancy that exceeds acceptable limits should be recorded on the batch records and investigated, and the batch quarantined until its status has been determined.

115. Results of any inspection and testing should be assessed against documented, pre-determined standards / specifications and appropriate records maintained. Where results fall outside this standards / specifications, further investigation and / or appropriate corrective action should be taken and appropriate records maintained.

116. When any new manufacturing formula or method of preparation is adopted, or when there are any significant amendments to the manufacturing process, including any change in equipment or materials, which may affect product quality and / or the reproducibility of the process, steps should be taken to demonstrate its suitability for routine processing. The defined process, using the materials and equipment specified, should be shown to yield a product consistently of the required quality.

Contamination Control

117. Where operations on different products are carried out simultaneously or consecutively in the same room, and where this is a product quality or safety issue, there should be measures in place to prevent mix-up and / or cross-contamination.

118. Checks should be carried out to ensure that transfer lines and other pieces of equipment used for the transportation of veterinary premixes from one area to another are clean before use and are connected in a correct manner.

119. Good manufacturing practice should recognize and address the potential for contamination of veterinary premixes with incompatible raw materials resulting from the order in which veterinary premixes are manufactured. This must be done with an adequate understanding of the operational limits of the manufacturing equipment and the particular quality and safety risks that apply to a particular material in a particular veterinary premixes. Strategies adopted to address this may include flushing, sequencing and cleaning. The procedures adopted to address these risks should be documented and verified through inspection, sampling and testing.

120. Precautions should be taken to ensure carry-over from previous mixing of veterinary premixes does not contaminate subsequent product mixes.

121. Out-loading and packaging systems including all fixed or mobile silos, bins and tanks should be designed and operated to prevent contamination, unintended mixing or misidentification of finished product. Key elements of this system are that :

- the bins (silos, tanks, etc.) should be identified by an appropriate labelling or numbering system;
- product stored within a given bin (silo, tank, etc.) should be identified via documentation and records;
- bins (silos, tanks, etc.) should be designed to be free-flowing, readily inspected and cleaned, and should be able to be sealed and secured.

122. At every stage of processing, products and materials should be protected from microbial and other contamination. Special attention needs to be paid to the prevention of microbial contamination during manufacture or storage of susceptible liquid formulations.

Quality Control

123. Manufacturers of veterinary premixes must have in place an effective quality control system which is designed to ensure that before products are released from manufacturer for supply, they meet specifications and have been manufactured in accordance with the manufacturer's documented procedures.

124. Quality Control is concerned with sampling, specifications and testing as well as the organization, documentation and release procedures which ensure that the necessary and relevant tests are carried out, and that materials are not released for use, nor products released for sale or supply, until their quality has been judged satisfactory.

125. A quality control system should be supervised by a person with appropriate qualifications and experience, who is responsible to the management and independent of the other divisions of the manufacturing operation.

126. The quality control department should be empowered to take samples from any part of the manufacturing processes or finished product at any time.

Sampling and Reference / Retention Samples

127. There should be written procedures for sampling, which include the person(s) authorized to take samples, the methods and equipment to be used, the amounts to be taken, instructions for any required sub-division of the sample, the type and condition of the sample container to be used, the identification of containers sampled, the storage conditions, instructions for the cleaning and storage of sampling equipment and any precautions to be observed to avoid contamination of the material or any deterioration in its quality.

128. Reference / retention samples should be representative of the batch of materials or products from which they are taken. Other samples may also be taken to monitor the most stressed part of a process (e.g. beginning, middle or end of a process).

129. Reference / 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.

130. Reference / retention samples of starting materials (other than solvents, gases or water used in the manufacturing process) should be retained for at least two years after the release of the veterinary premixes, if their stability allows. That period may be shortened if the period of stability of the material, as indicated in the relevant specification is shorter. Packaging materials should be retained for the duration of the shelf life of the finished product concerned.

131. Reference / retention samples from each batch of finished veterinary premixes should be retained for at least one year after the expiry date. Finished products should be kept in their final packaging and stored under the recommended conditions.

132. For finished products, in many instances the reference and retention samples will be presented identically, i.e. as fully packaged units. In such circumstances, reference and retention samples may be regarded as interchangeable.

133. All reference / retention samples should bear a label indicating the content, identification / batch number, material supplier, date of sampling and the container from which samples have been drawn. Samples taken should be easily retrievable.

134. In all cases, the container used for storage should be composed of the same material as the market primary container in which the product is marketed.

135. Where practicable, these samples should be kept in their final packaging. It is recognized that because of the large volume of certain veterinary premixes in their final packaging, it may not be feasible for manufacturers to retain samples from each batch in its final packaging. However, manufacturers should ensure that sufficient representative samples of each batch are retained and stored in accordance with the guide.

136. Records of traceability of samples should be maintained and be available for review by Competent Authorities.

Testing

137. All testing operations described in the Marketing Authorization should be carried out according to the approved methods. Analytical methods should be validated.

138. There should be written procedures for testing materials and products at different stages of manufacture, describing the methods and equipment to be used.

139. The tests performed should be recorded and the records should include at least the following data :

- name of the material or product and, where applicable, dosage form;
- batch number and, where appropriate, the manufacturer and / or supplier;
- references to the relevant specifications and testing procedures;
- test results, including observations and calculations, and reference to any Certificates of Analysis;
- dates of testing;
- initials of the persons who performed the testing;
- initials of the persons who verified the testing and the calculations, where appropriate;
- a clear statement of release or rejection (or other status decision) and the dated signature of the designated responsible person.

140. The results obtained should be recorded and checked to make sure that they are consistent with each other. Any calculations should be critically examined.

141. All the in-process controls, including those made in the production area by production personnel, should be performed according to methods approved by Quality Control and the results recorded.

142. Where necessary, the date of receipt of any substance used for testing operations (e.g. reagents and reference standards) should be indicated on the container. Instructions for use and storage should be followed. In certain cases it may be necessary to carry out an identification test and / or other testing of reagent materials upon receipt or before use.

143. Where process water is used, a water quality manual should be prepared. Process water should be tested at a frequency consistent with the history of successful control. Sampling procedures should include 'worst case' sample points and production conditions. The sample size tested should be sufficient to demonstrate process control.

On-Going Stability Programme

144. The on-going stability programme helps to monitor the product over its shelf life and to determine that the product remains, and can be expected to remain, within specifications under the labelled storage conditions.

145. The on-going stability programme should be described in a written protocol and its results formalized as a report. The equipment used for the on-going stability programme (stability chambers among others) should be maintained.

146. The protocol for an on-going stability programme should extend to the end of the shelf life period and should include, but not be limited to, the following parameters :

- number of batch(es) per strength and different batch sizes, if applicable;
- relevant physical, chemical, microbiological and biological test methods;
- acceptance criteria;
- reference to test methods;
- description of the container closure system(s);
- testing intervals (time points);
- description of the conditions of storage;
- other applicable parameters specific to the veterinary premixes.

147. The number of batches and frequency of testing should provide a sufficient amount of data to allow for trend analysis. Unless otherwise justified, at least one batch per year of veterinary premixes manufactured in every strength and every primary packaging type, if relevant, should be included in the stability programme (unless none are produced during that year).

148. In certain situations, additional batches should be included in the on-going stability programme. For example, an on-going stability study should be conducted after any significant change or significant deviation to the process or package. Any reworking, reprocessing or recovery operation should also be considered for inclusion.

149. Results of the on-going stability studies should be recorded. Out of specification or significant atypical trends should be investigated. Any confirmed out of specification result, or significant negative trend, should be reported to the Competent Authority.

150. A summary of all the data generated, including any interim conclusions on the programme, should be written and maintained. This summary should be subjected to periodic review.

Inspection of Suppliers

151. Appropriate assurance of the reliability and quality of vendors and their materials should be maintained.

Contract Manufacture / Analysis

152. Contract manufacture / analysis must be correctly defined, agreed and controlled in order to avoid misunderstandings which could result in a product or work of unsatisfactory quality. There must be a written contract between the Contract Giver and the Contract Acceptor which clearly establishes the duties of each party. The contract must clearly state the way in which the authorized person releasing each batch of product for sale exercises his full responsibility.

153. Where any part of the manufacture / analysis of veterinary premixes are contracted to another party, the manufacturer should ensure that before manufacture / analysis commences, all parties have signed a written agreement that clearly specifies each party's responsibility in relation to every aspect of the manufacturing process, assurance of product quality and consistency with product registration particulars.

154. Arrangements for contracted steps of manufacture / analysis should not compromise the quality of the product. All arrangements for manufacture / analysis must be in accordance with the Marketing Authorization and agreed by both parties.

155. The contract should specify the way in which the authorized person releasing the batch for sale ensures that each batch has been manufactured and checked for compliance with the requirements of Marketing Authorization.

156. The contract should describe clearly who is responsible for purchasing materials, testing and releasing materials, undertaking production and quality controls, including in-process controls, and who has responsibility for sampling and analysis. In the case of contract analysis, the contract should state whether or not the Contract Acceptor should take samples at the premises of the manufacturer.

157. The contract should permit the Contract Giver to visit the facilities of the Contract Acceptor.

158. In case of contract analysis, the Contract Acceptor should understand that he is subject to inspection by the Competent Authority.

Complaints and Product Recall

159. All complaints and other information concerning potentially defective products must be carefully reviewed according to written procedures. In order to provide for all contingencies, a system should be designed to recall, if necessary, promptly and effectively products known or suspected to be defective from the market.

160. A person should be designated responsible for handling the complaints and deciding the measures to be taken together with sufficient supporting staff to assist him / her.

161. There should be written procedures describing the action to be taken, including the need to consider a recall, in the case of a complaint concerning a possible product defect.

162. Any complaint concerning a product defect should be recorded with all the original details and thoroughly investigated. The person(s) responsible for production and quality control should normally be involved in the study of such problems.

163. If a product defect is discovered or suspected in a batch, consideration should be given to checking other batches should be checked in order to determine whether they are also affected. In particular, other batches which may contain reworks of the defective batch should be investigated.

164. All the decisions and measures taken as a result of a complaint should be recorded and referenced to the corresponding batch records.

165. Complaints records should be reviewed regularly for any indication of specific or recurring problems requiring attention and possibly the recall of marketed products.

166. The Competent Authorities should be informed if a manufacturer is considering action following possibly faulty manufacture, product deterioration or any other serious quality problems with a product.

167. The execution and coordination of recalls should also be handled by a designated person with supported by sufficient staff in order to handle all aspects of the recalls with the appropriate degree of urgency. This responsible person should normally be independent of the sales and marketing organization.

168. There should be established written procedures, regularly checked and updated when necessary, in order to organize any recall activity.

169. Recall operations should be capable of being initiated promptly and at any time, inside or outside working hours and should therefore include emergency and ‘out of hours’ contact person and telephone numbers.

170. All Competent Authorities of all countries to which products may have been distributed should be informed promptly if products are intended to be recalled because they are, or are suspected of, being defective.

171. The distribution records should be readily available to the person(s) responsible for recalls, and should contain sufficient information on wholesalers and directly supplied customers (with addresses, phone and / or fax numbers inside and outside working hours, batches and amounts delivered), including those for exported products and medical samples.

172. Recalled products should be identified and stored separately in a secure area while awaiting a decision on their fate.

173. The progress of the recall process should be recorded and a final report issued, including reconciliation between the delivered and recovered quantities of the products.

174. The effectiveness of the arrangements for recalls should be evaluated regularly.

Internal Audit / Self Inspection

175. Manufacturers of veterinary premixes should regularly and systematically carry out internal audits / self inspection of all aspects of their manufacturing operations, as well as of their quality assurance program, in order to monitor compliance with their authorized procedures, standards and requirements, and to ensure product quality. Steps should be taken to implement any necessary corrective and preventive action identified by those internal audits and to assess the outcomes. All related records should be maintained.

176. Internal audit / self inspections should be conducted in an independent and detailed way by designated competent person(s) from the company. Independent audits by external experts may also be useful.

Glossary of some terms used

Definitions given below apply to the words as used in this Guide. They may have different meanings in other contexts.

Air-lock
An enclosed space with two or more doors, and which is interposed between two or more rooms, e.g. of differing class of cleanliness, for the purpose of controlling the air-flow between those rooms when they need to be entered. An air-lock is designed for and used by either people or goods (PAL – personnel air-lock; MAL – material air-lock).

Authorized person
Person recognized by the authority as having the necessary basic scientific and technical background and experience.

Batch (or lot)
A defined quantity of starting material, packaging material or product processed in one process or series of processes so that it could be expected to be homogeneous.

Note : To complete certain stages of manufacture, it may be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch. In the case of continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity.

For the control of the finished product, a batch of products comprises all the units of a pharmaceutical form which are made from the same initial mass of material and have undergone a single series of manufacturing operations or, in the case of a continuous production process, all the units manufactured in a given period of time.

Batch number (or lot number)
A distinctive combination of numbers and / or letters which specifically identifies a batch.

Bulk product
Any product which has completed all processing stages up to, but not including, final packaging.

Calibration
The set of operations which establish, under specified conditions, the relationship between values indicated by a measuring instrument or measuring system, or values represented by a material measure, and the corresponding known values of a reference standard.

Computerised system
A system including the input of data, electronic processing and the output of information to be used either for reporting or automatic control.

Cross-contamination
Contamination of a starting material or of a product with another material or product.

Finished product
A product which have undergone all stages of production, including packaging in its final container.

In-process control
Checks performed during production in order to monitor and if necessary to adjust the process to ensure that the product conforms to its specification. The control of the environment or equipment may also be regarded as a part of in-process control.

Intermediate product
Partly processed material which must undergo further manufacturing steps before it becomes a bulk product.

Manufacture (maybe interchangeable with Production)
All operations of purchase of materials and products, Production, Quality Control, release, storage, distribution of products and the related controls.

Packaging
All operations including filling and labelling which a bulk product has to undergo in order to become a finished product.

Production (maybe interchangeable with Manufacture)
All operations involved in the preparation of a product, from receipt of materials, through processing and packaging, to its completion as a finished product.

Quarantine
The status of starting or packaging materials, intermediate, bulk or finished products isolated physically or by other effective means whilst awaiting a decision on their release or refusal.

Reconciliation
A comparison, making due allowance for normal variation, between the amount of product or materials theoretically and actually produced or used.

Reference sample
A sample of a batch of starting material, packaging material or finished product which is stored for the purpose of being analyzed should the need arise during the shelf life of the batch concerned. Where stability permits, reference samples from critical intermediate stages (e.g. those requiring analytical testing and release) or intermediates that are transported outside of the manufacturer's control should be kept.

Reprocessing
The treatment of a batch of product of unacceptable quality by repeating the same process steps from a defined stage of production so that its quality may be rendered acceptable.

Retention sample
A sample of a fully packaged unit from a batch of finished product with information for example, presentation, packaging, labelling, patient information leaflet, batch number and expiry date which is stored for identification purposes should the need arise during the shelf life of the batch concerned. There may be exceptional circumstances where this requirement can be met without retention of duplicate samples e.g. where small amounts of a batch are packaged for different markets or in the production of very expensive medicinal products.

Return
Sending back to the manufacturer or distributor of a product which may or may not present a quality defect.

Reworking
The treatment of a batch of product of unacceptable quality by using a process other than that used to produce the original product which defer from a defined stage of production so that its quality may be made acceptable.

Note: Reworking may be carried out for products that have been rejected as well as those that have not been rejected following approval. The reworked batches are subject to stringent quality controls. It must be demonstrated that reworking has no negative influence on the product concerned.

Starting material
Any substance used in the production of a product including raw materials and packaging materials.

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