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May 30, 2003

03-106392-230

TO: ASSOCIATIONS

I am pleased to inform you that a Veterinary Drugs Annex to the Good Manufacturing Practices (GMP) Guidelines, developed in consultation with stakeholders, is now available on the Health Products and Food Branch Inspectorate website at the following address:

www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate

The document is divided in 2 parts, Veterinary drugs and Drug premixes, and describes interpretations that differ from the main GMP Guidelines. The numbering of each interpretation used in this Annex corresponds to that of the interpretation being modified from the current GMP Guidelines. Unless otherwise stated in this Annex, all interpretations included in the GMP Guidelines are applicable to Veterinary drugs and Drug premixes.

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VETERINARY DRUGS ANNEX TO CURRENT EDITION OF THE GOOD MANUFACTURING PRACTICES GUIDELINES

Supersedes:**New document**

Date issued: May 1st , 2003

Date of implementation: July 1st , 2003

Ce document est aussi disponible en français

Canada

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INTRODUCTION

This Annex to the current edition of the Good Manufacturing Practices (GMP) Guidelines is intended to clarify certain aspects that have relevance to the manufacture of veterinary drugs and were developed by Health Canada in consultation with their stakeholders. For the purpose of this Annex, GMP Guidelines means the current edition of GMP Guidelines. Although the Regulations and their rationale as well as the quality management principles outlined in the GMP Guidelines apply to all veterinary drugs, it is recognized that some of the interpretations provided in the GMP Guidelines may not always be applicable or appropriate in certain situations (e.g. premises for fabrication of veterinary drugs containing penicillin) or to the manufacture of drug premixes. For this particular type of veterinary drugs, feed ingredients are used in large quantities and invariably contain some light, powdery, flour like material, which may lead to extremely dusty conditions. This problem can be controlled with sophisticated dust extraction equipment. However, the main concern in the production of drug premixes is the potential for cross-contamination. Also, the production methods and handling characteristics of drug premixes do not necessarily call for the same complex techniques requiring highly skilled production and control staff as those required for other veterinary drugs. For that reason this Annex is separated in two sections. Section 1 addresses veterinary drugs with the exception of drug premixes and Section 2 addresses drug premixes only.

SCOPE

1. The guidance included in Sections 1 and 2, when placed in context with the GMP Guidelines, should facilitate compliance with Division 2 of the *Food and Drug Regulations*. In order to avoid repetition, only those interpretations that are different from the ones included in the GMP Guidelines are contained in this Annex. The numbering of each interpretation used in this Annex corresponds to that of the interpretation being modified from the GMP Guidelines. Therefore, unless otherwise stated in this Annex, all interpretations included in the GMP Guidelines are applicable to veterinary drugs.

2. The modified interpretations from GMP Guidelines contained in Section 1 of this Annex apply specifically to all veterinary drugs with the following exceptions:

    2.1 Dilute Premix and Medicated Feed as per C.01A.001 (2).
    2.2 Veterinary biologics regulated under the *Animal Disease and Protection Act* and Regulations or other legislation.
    2.3 Drug Premixes (See Section 2)

1. The modified interpretations from GMP Guidelines contained in Section 2 of this Annex apply specifically to Drug Premixes. They do not apply to:

    3.1 Premixes containing only vitamin and mineral ingredients as these preparations are not considered to be drugs and are regulated by the Feeds Act (Agriculture Canada).
    3.2 Any other veterinary drugs.

The content of this Annex should not be regarded as the only interpretation of the GMP Regulations nor does it intend to cover every conceivable case. Alternative means of complying with these Regulations can be considered with the appropriate scientific justification. Different approaches may be called for as new technologies emerge.

GLOSSARY OF TERMS

The following definitions are provided to complement those already available under the Glossary of Terms of the GMP Guidelines.

DRUG PREMIX (or Medicated Premix) (prémelange médicamenteux) - A drug for veterinary use to which a drug identification number has been assigned, where the directions on its label specify that it is to be mixed with feed as defined in section 2 of the *Feeds Act*. (C.01A.001 of the *Food and Drugs Regulations*). It is a veterinary drug product prepared in advance with a view to the subsequent manufacture of medicated feeds.

DILUTE DRUG PREMIX (prémelange médicamenteux dilué) - A drug for veterinary use that results from mixing a drug premix with a feed as defined in section 2 of the *Feeds Act*, to such a level that at least 10 kg of the resulting mixture is required to medicate one tonne of complete feed, as defined in section 2 of the *Feeds Regulations*, 1983, with the lowest approved dosage level of the drug.

MEDICATED FEED (aliment médicamenteux) - A mixed feed that contains a medicating ingredient [2.(1) of the *Feeds Regulations*, 1983]

FEED INGREDIENT (ingrédient pour aliment) - Any substance or mixture of substance that is assessed or evaluated as being acceptable for use in feeds.

SECTION 1: VETERINARY DRUGS EXCEPT DRUG PREMIXES

MODIFIED INTERPRETATIONS FROM GMP GUIDELINES

PREMISES

C.02.004

11.2 Campaign production can be accepted on a product by product basis where proper justification is provided, rigorous validation is conducted, and validated controls and monitoring are in place to minimize any risk of cross-contamination.

In the case of facilities producing other veterinary drugs, campaign production of veterinary drugs containing penicillin is considered acceptable provided that the following conditions are met:

- non-penicillin drug products for human use are not fabricated, packaged/labeled or stored in the same facility.

- validated decontamination and cleaning procedures are in place to minimize any risk of cross-contamination.

RAW MATERIAL TESTING

C.02.009

6.3 It is permissible to sample only a proportion of the containers for identity testing where a validated procedure has been established to ensure that no single container of API has been incorrectly labelled.

This validation should take account of at least the following aspects:
- the nature and status of the manufacturer and of the supplier and their understanding of the GMP requirements of the Pharmaceutical Industry;
- the Quality Assurance system of the manufacturer of the API;
- the manufacturing conditions under which the API is produced and controlled;
- the nature of the API and the medicinal products in which it will be used.

FINISHED PRODUCTS TESTING

C.02.018

Note: For certain topical non-Schedule and cosmetic type products (e.g., hoof ointment) that contain only ingredients such as oils, tars and other emollients, it may be acceptable to perform identity tests based on the physical characteristics of the products such as specific gravity or viscosity. In these circumstances, there must be an attestation from the fabricator certifying that the addition of the ingredients in question was witnessed in the manufacturing process .

SECTION 2: DRUG PREMIXES

MODIFIED INTERPRETATIONS FROM GMP GUIDELINES

PREMISES

C.02.004

2. The premises are designed, constructed and maintained such that they minimize entry of insects and other animals and the migration of extraneous material from the outside into the building and from one area to another.

   2.1 Doors, windows, walls, ceilings and floors are free of undue openings or cracks.

   2.2 Doors giving direct access to the exterior from manufacturing and packaging areas are used for emergency purposes only. Receiving and shipping area(s) do not allow direct access to production areas.

3. In all areas where raw materials, in-process drug premixes, or drug premixes are exposed, the following considerations apply to the extent necessary to prevent contamination.

   3.1 Floors, walls, and ceilings permit cleaning. Surface materials which shed particles are avoided.

   3.2 Floors, walls, ceilings, and other surfaces are made of hard and smooth materials.

   3.3 Joints between walls, ceilings, and floors do not permit the accumulation of extraneous materials.

   3.5 Floor drains are screened and trapped, as necessary, or sealed when not in use.

   3.6 Air quality is maintained through dust control, and periodic verification and replacement of air filters. Air handling systems provide adequate control of airborne dust and are subject to periodic verification to ensure compliance with their design specifications. Records are kept.

   Specific attention is given to the need to avoid cross-contamination and facilitate cleaning.

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

11.2 Campaign production can be accepted on a product by product basis where proper justification is provided, rigorous validation is conducted, and validated controls and monitoring are in place to minimize any risk of cross-contamination.

   In the case of facilities producing other veterinary drugs, campaign production of drug premixes containing penicillin is considered acceptable provided that the following conditions are met:

   - non-penicillin drug products for human use are not fabricated, packaged/labeled or stored in the same facility.

   - validated decontamination and cleaning procedures are in place to minimize any risk of cross-contamination.

SANITATION

C.02.007

3.1 Cleaning procedures for manufacturing equipment are effective.

Cleaning procedures for equipment used in the campaign production of drug premixes containing penicillin are validated.

3.4 Analytical methods used to detect penicillin residues are validated.

5. The manufacture of drug premixes is conducted in segregated areas. Whenever possible, such segregated areas do not form part of a main manufacturing plant. Segregated areas surrounded by a buffer zone in order to minimize the risk of contamination of other manufacturing areas are considered an acceptable alternative.

Use of unit or portable dust collectors are avoided in fabrication areas, especially in dispensing, unless the effectiveness of their exhaust filtration is demonstrated and the units are regularly maintained as per written approved procedures.

RAW MATERIAL TESTING

C.02.009

3. This interpretation does not apply.

6. A sample of each lot of raw material is fully tested against its specifications. Sampling is conducted according to a statistically valid plan.

6.1 In addition, for API, each sample taken as part of the sampling plan is tested for the identity of its content using a specifically discriminating identity test.

In lieu of testing each sample referred to in section 6.1, a composite sample is acceptable as long as the following conditions are met:

6.1.1 each composite sample should be made of no more than 10 samples; and

6.1.2 a potency test is performed on each composite sample to establish the mass balance of the composite sample.

6.2 APIs originating from a dedicated facility that fabricates only one ingredient are exempted from the requirements outlined under Interpretation 6.1, provided that no re-packaging or re-labelling has taken place.

6.3 It is permissible to sample only a proportion of the containers for identity testing where a validated procedure has been established to ensure that no single container of API has been incorrectly labelled.

This validation should take account of at least the following aspects:

- the nature and status of the manufacturer and of the supplier and their understanding of the GMP requirements of the Pharmaceutical Industry;
- the Quality Assurance system of the manufacturer of the API;
- the manufacturing conditions under which the API is produced and controlled;
- the nature of the API and the medicinal products in which it will be used.

C.02.010

2. Identity testing is conducted on all lots of any raw material received on the premises of the person that formulates the raw material into drug premixes. This test is specific except for feed ingredients where only non specific identity tests may exist.

   This identity testing is performed in accordance with C.02.009, interpretation 6.

8. *Except for feed ingredients*, if the same batch of raw material is subsequently received, this batch is also considered as separate for sampling, testing and release. However, full testing to specifications may not be necessary provided that all the following conditions are met:

   8.1 a specifically discriminating identity test is conducted;
   8.2 the raw material has not been repackaged or relabelled;
   8.3 the raw material is within the re-test date assigned by the vendor;
   8.4 evidence is available to demonstrate that all pre-established transportation and storage conditions have been maintained.

MANUFACTURING CONTROL

C.02.011

2. All processes that affect content uniformity and potency are validated.

PACKAGING MATERIALTESTING

C.02.016

2. Specifications are in compliance with the marketing authorization.

3. The adequacy of test or examination methods is established and documented.

SAMPLES

C.02.025

2. A sample of each lot or batch of API is retained by the fabricator of the drug premix.

STABILITY

C.02.028

1.1 At least one lot of each drug premix is enrolled in the continuing stability program at all times.