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To promote good nutrition and informed use of drugs, food, medical devices and natural health products, and to maximize the safety and efficacy of drugs, food, natural health products, medical devices, biologics and related biotechnology products in the Canadian marketplace and health system.

Health Products and Food Branch Inspectorate

Guidance Document Annex 4 to the Current Edition of the Good Manufacturing Practices Guidelines – Veterinary Drugs

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1.0 Introduction

This Annex to the current edition of the “Good Manufacturing Practices (GMP) Guidelines (GUI-0001)” (<http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0001-eng.php>) 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 the GMP Guidelines (GUI-0001). Although the *Food and Drug Regulations* (<http://laws-lois.justice.gc.ca/eng/C.R.C.-c.870/index.html>) and their rationale as well as the quality management principles outlined in the GMP Guidelines (GUI-0001) apply to all veterinary drugs, it is recognized that some of the interpretations provided in the GMP Guidelines (GUI-0001) may not always be applicable or appropriate in certain situations (for example, 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 for other veterinary drugs. For that reason this Annex is separated in three Sections.

The revisions to this Annex include addition of a Section 2 for non-sterile, non-prescription veterinary drugs that require no withdrawal period at the highest dosage in each species for which they are approved.

The guidance included in this Annex when placed in context with the GMP Guidelines (GUI-0001), 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 (GUI-0001) 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 (GUI-0001). **Therefore, unless otherwise stated in this Annex, all interpretations included in the GMP Guidelines (GUI-0001) are applicable to all veterinary drugs.**

The content of this Annex should not be regarded as the only interpretation of Division 2 of the *Food and Drug Regulations* (GMP) 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.

2.0 Purpose

To provide additional interpretive guidance for Part C, Division 2, of the *Food and Drug Regulations* for veterinary drugs. These guidelines are designed to facilitate compliance by the regulated industry and to enhance consistency in the application of the regulatory requirements.

3.0 Scope

The Annex does not apply to:

- Veterinary biologics regulated under the *Health of Animals Act* (<http://laws-lois.justice.gc.ca/eng/H-3.3/index.html>) and *Regulations* (<http://laws-lois.justice.gc.ca/eng/C.R.C.-c.296/index.html>) or other legislation);
- Dilute Premix and Medicated Feed as per C.01A.001 (2) of the *Food and Drug Regulations*; and
- Premixes containing only vitamin and mineral ingredients as these preparations are not considered to be drugs and are regulated by the *Feeds Act* (<http://laws-lois.justice.gc.ca/eng/F-9/index.html>).

Section 1 of this Annex applies to all veterinary drugs except for non-sterile, non-prescription^{1 2} veterinary drugs with no withdrawal period addressed in Section 2, and drug premixes covered in Section 3. For non-segregated facilities that manufacture more than one class of drugs covered by this Annex, the most stringent interpretation would apply

4.0 Section 1: All veterinary drug products except Section 2 Drugs and Drug Premixes

4.1 Modified interpretations from the Good Manufacturing Practices Guidelines (GUI-0001)

Premises

C.02.004

- 11.1 Campaign production can be accepted on a product by product basis where proper justification is provided, 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/labelled or stored in the same facility; and
- validated decontamination and cleaning procedures are in place to minimize any risk of cross-contamination.

Raw Material Testing

C.02.009

2. Specifications of active pharmaceutical ingredients (API) are of pharmacopeial or other equivalent standards and are in compliance with the marketing authorization. Specifications of other raw materials may be based on a house standard provided that they are in compliance with the current marketing authorization of the drug.

¹**C.01.046.** A person may sell a drug listed or described in *Part II of Schedule F* to the *Regulations*, without having received a prescription therefore, if

(a) the drug is in a form not suitable for human use; or
(b) the principal display panel of both the inner label and the outer label carries, in both official languages, the statement "For Veterinary Use Only/Pour usage vétérinaire seulement" or "Veterinary Use Only/Usage vétérinaire seulement", immediately following or preceding the brand name, proper name or common name, in type size not less than one-half as large as the largest type on the label.

²All veterinary drugs that contain a substance(s) listed on *Part I of Schedule F* are required by the *Food and Drugs Regulations* to be sold pursuant to a prescription by a licensed veterinarian. For this Annex, prescription drugs are required under the *Food and Drugs Regulations* to contain "Pr" in the upper left quarter of the principal display panel on the drug's final packaging.

5.0 Section 2: Non-Prescription, non-sterile veterinary drugs that require no withdrawal period at the highest dosage in each species which they are approved

5.1 Modified interpretations from the Good Manufacturing Practices Guidelines (GUI-0001)

The modified interpretations from the GMP Guidelines (GUI-0001) contained in this Section apply to non-sterile, non-prescription veterinary drugs that have a zero withdrawal period for **all** approved species for which a Drug Identification Number (DIN) is issued. These include products such as topical creams, udder washes, teat dips, external antiseptics, external parasiticides and oral paste for horses.

Premises

C.02.004

7. Utilities and support systems (for example, Heating, Ventilating and Air Conditioning (HVAC), dust collection, and supplies of purified water, steam, compressed air, nitrogen) for buildings in which drugs are fabricated or packaged/labelled are of adequate design and are appropriately maintained for its intended purpose.

Equipment

C.02.005

- 5.3 Equipment used during the critical steps of fabrication, packaging/labelling, and testing, including computerized systems, is suitable for its intended purpose.

Personnel

C.02.006

1. The interpretation applies to fabricators, packagers/labellers, and testers. The interpretation has been modified as follows for distributors and importers:

For distributors and importers, individuals in charge of the quality control department:

- are qualified by pertinent academic training and experience (possession of a diploma, certificate or other evidence of formal qualifications awarded on completion of a course of study at a university, college or technical institute in a science related to the work being carried out combined with at least two years of relevant practical experience); and
- while remaining accountable for those duties and responsibility, can delegate their duties and responsibilities to a person who is qualified by pertinent academic training and experience.

Sanitation

C.02.007

- 3.1 Cleaning procedures for all primary contact surfaces for manufacturing and filling equipment should consistently result in the absence of any visible product or cleaning agent residues. The equipment should be kept clean and dry and protected from contamination.

- 3.4 If analytical methods are used to detect residues or contaminants, they have been shown to provide accurate and consistent results.

C.02.008

- 1.1 Personnel must undergo a health examination prior to having access to areas where drug is exposed during its fabrication or packaging/labelling. The Note under Section 1.1 in GMP Guidelines (GUI-0001) applies.

Raw Material Testing

C.02.009

2. Specifications of API are of pharmacopeial or other equivalent standards and are in compliance with the marketing authorization. Specifications of other raw materials may be based on a house standard provided that they are in compliance with the current marketing authorization of the drug.
4. Water used in the formulation of any drug product for which there is a pharmacopeial (Schedule B of the *Food and Drugs Act*) (<http://laws-lois.justice.gc.ca/eng/F-27/page-4.html#anchors:2>) monograph meets the requirements of the applicable monograph.

For drugs not appearing in a pharmacopeial (Schedule B of the *Food and Drugs Act*) monograph, water used in the formulation must meet appropriate specifications based on sound physical and chemical principles. In addition, specifications should include requirements for total microbial count, which should not exceed 100 Colony-forming unit (cfu)/ml, and for absence of *Escherichia coli* and *Salmonella* for oral preparations and *Staphylococcus aureus* and *Pseudomonas aeruginosa* for topical preparations

5. Test methods provide accurate and consistent results.
- 6.1 In addition, each container of a lot of an API is tested for the identity of its contents using a specifically discriminating identity test.

Manufacturing Control

C.02.011

2. All critical production processes have been shown to produce consistent results and are approved by the person in charge of the quality control department. Demonstration of consistency should include a satisfactory evaluation of completed batch documents, in-process controls, finished product test results, and additional testing as appropriate for at least 3 consecutive batches.
3. A written report recording results and conclusions of the evaluation of critical production processes is prepared, evaluated, approved, and maintained.
4. Changes to production processes, equipment, or materials that may affect product quality and/or process reproducibility are evaluated for suitability prior to implementation.
9. Provided that changeover procedures are evaluated and approved prior to implementation, similar non-medicinal products may be fabricated or packaged/labelled in areas or with equipment that is also used for the production of pharmaceutical products.

Finished Products Testing

C.02.018

All test methods have been shown to provide accurate and consistent results according to the marketing authorization.

Note: For certain topical non-Schedule products (for example, hoof ointment) that contain only ingredients such as oils, tars and other emollients, it may be acceptable to perform 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.

Stability Testing

C.02.027

1. The stability of the drug is determined prior to marketing and prior to adoption of significant changes in formulation, fabrication procedures, or packaging materials that may affect the shelf life of the drug. Stability samples should be stored at conditions supportive of the intended label storage conditions.
 - 1.1 Accelerated stability data and/or data from similar product formulations are considered to be preliminary information only. The assignment of the expiry date may be initially based on accelerated data and data from similar formulations, and is supported by long term testing.
 - 1.3 For existing chemical entities (for example, veterinary drugs other than new drugs), one commercial-scale batch of each strength is sampled. The principle of bracketing and matrixing designs may be applied if justified.
 - 1.7 Analytical test procedures used in stability evaluation have been shown to provide accurate and consistent results. Assays are to be stability-indicating, (for example, sufficiently specific to detect and quantify degradation products and to distinguish between degraded and non-degraded materials). Limits for individual specified, unspecified, and total degradation products complies with the marketing authorisation.

C.02.028

- 1.2 A minimum of one batch of every strength of the drug is enrolled in the continuing stability program at all times. The principle of bracketing and matrixing designs may be applied if justified in accordance with the approved marketing authorization.
2. Minor changes of minor excipients (for example, addition, deletion, or substitution of a fragrance or flavour) to the formulations may be acceptable without new stability data, provided that ongoing stability studies are conducted on the revised formulation to demonstrate that the proposed change does not affect the quality of the drug product. These studies may be conducted concurrently with the marketing of the modified product.

6.0 Section 3: Drug Premixes

6.1 Modified interpretations from the Good Manufacturing Practices Guidelines (GUI-0001)

Premises

C.02.004

2. The premises are designed, constructed and maintained such that they minimize entry of pests 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, primary packaging materials, 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.
7. Utilities and support systems (for example, HVAC, dust collection, and supplies of purified water, steam, compressed air, nitrogen) for buildings in which drugs are fabricated or packaged/labelled are of adequate design and are appropriately maintained for its intended purpose.
- 11.1 Campaign production can be accepted on a product by product basis where proper justification is provided, 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; and
- validated decontamination and cleaning procedures are in place to minimize any risk of cross-contamination.

11.2 This interpretation does not apply.

11.3 This interpretation does not apply.

11.4 Work areas used for the production or storage of drug premixes or components thereof shall not be used for, and shall be physically separated from work areas used for the manufacture and storage of fertilizers, herbicides, insecticides, fungicides, rodenticides, and other pesticides.

Equipment

C.02.005

3.4 Equipment is located so that production operations undertaken in a common area are compatible and cross-contamination between such operations is prevented. Equipment used for the production or storage of drug premixes or components thereof shall not be used for, and shall be physically separated from equipment used for the manufacture and storage of fertilizers, herbicides, insecticides, fungicides, rodenticides, and other pesticides.

5.3 Equipment used during the critical steps of fabrication, packaging/labelling, and testing, including computerized systems, is suitable for its intended purpose.

Personnel

C.02.006

1. The interpretation applies to fabricators, packagers/labellers, and testers. The interpretation has been modified as follows for distributors and importers:

For distributors and importers, individuals in charge of the quality control department:

- are qualified by pertinent academic training and experience (possession of a diploma, certificate or other evidence of formal qualifications awarded on completion of a course of study at a university, college or technical institute in a science related to the work being carried out combined with at least two years of relevant practical experience); and
- while remaining accountable for those duties and responsibility, can delegate their duties and responsibilities to a person who is qualified by pertinent academic training and experience.

Sanitation

C.02.007

3.1 Cleaning procedures for all primary contact surfaces for manufacturing and filling equipment should consistently result in the absence of any visible product or cleaning agent residues. The equipment should be kept clean and dry and protected from contamination.

- 3.4 If analytical methods are used to detect residues or contaminants, they have been shown to provide accurate and consistent results. Analytical methods used to detect penicillin residues are validated. Guidance on analytical method validation can be obtained from the *International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Products* (VICH) (<http://www.vichsec.org/>) publications such as *VICH-GL-1 Validation of Analytical Procedures: Definition and Terminology* (http://www.vichsec.org/pdf/gl01_st7.pdf) and *VICH-GL-2 Validation of Analytical Procedures: Methodology* (http://www.vichsec.org/pdf/gl02_st7.pdf) or in any standard listed in *Schedule B of the Food and Drugs Act*.
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.

C.02.008

- 1.1 Personnel must undergo a health examination prior to having access to areas where drug is exposed during its fabrication or packaging/labelling. The Note under Section 1.1 in GMP Guidelines (GUI-0001) applies.

Raw Material Testing

C.02.009

2. Specifications of API are of pharmacopeial or other equivalent standards and are in compliance with the marketing authorization. Specifications of other raw materials may be based on a house standard provided that they are in compliance with the current marketing authorization of the drug.
4. Water used in the formulation of any drug product for which there is a pharmacopeial (*Schedule B of the Food and Drugs Act*) monograph meets the requirements of the applicable monograph.

For drugs not appearing in a pharmacopeial (*Schedule B of the Food and Drugs Act*) monograph, water used in the formulation must meet appropriate specifications based on sound physical and chemical principles. In addition, specifications should include requirements for total microbial count, which should not exceed 100 cfu/ml, and for absence of *Escherichia coli* and *Salmonella* for oral preparations and *Staphylococcus aureus* and *Pseudomonas aeruginosa* for topical preparations.

- 6.1 In addition, each container of a lot of an API is tested for the identity of its contents using a specifically discriminating identity test.
- 6.4 Where a batch of any API, after leaving the site of its fabrication is handled in any substantial way (for example, repackaged by a third party) prior to its receipt on the premises of the person who formulates the API into dosage forms, each container in that batch is sampled and its contents positively identified.

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.

6. 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:
 - 6.1 a specifically discriminating identity test is conducted;
 - 6.2 the raw material has not been repackaged or relabelled;
 - 6.3 the raw material is within the re-test date assigned by the vendor;
 - 6.4 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.
3. A written report recording results and conclusions of the evaluation of critical production processes is prepared, evaluated, approved, and maintained.
4. Changes to production processes, equipment, or materials that may affect product quality and/or process reproducibility are evaluated for suitability prior to implementation.
9. Provided that changeover procedures are evaluated and approved prior to implementation, similar non-medicinal products may be fabricated or packaged/labelled in areas or with equipment that is also used for the production of pharmaceutical products.

Packaging Material Testing

C.02.016

2. Specifications are in compliance with the marketing authorization.
3. The adequacy of test or examination methods is established and documented.

Finished Product Testing

C.02.018

2. Test Methods are validated, and the results of such validation studies are documented. Method transfer studies are conducted when applicable.

Note: Guidance on analytical method validation can be obtained from publications such as *VICH-GL-1 Validation of Analytical Procedures: Definition and Terminology* and *VICH-GL-2*

Validation of Analytical Procedures: Methodology or in any standard listed in Schedule B of the Food and Drugs Act.

Samples

C.02.025 and C.02.026

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

Stability

C.02.027

- 1.7 Analytical test procedures used in stability evaluation have been shown to provide accurate and consistent results. Assays are to be stability-indicating, (for example, sufficiently specific to detect and quantify degradation products and to distinguish between degraded and non-degraded materials). Limits for individual specified, unspecified, and total degradation products complies with the marketing authorisation.

C.02.028

- 1.2 A minimum of one batch of every strength of the drug premix is enrolled in the continuing stability program at all times. The principle of bracketing and matrixing designs may be applied if justified and in accordance with VICH documents *VICH-GL-3 Stability Testing of New Veterinary Drug Substances* ([http://www.vichsec.org/pdf/2007/GL03_ST7\(R\).pdf](http://www.vichsec.org/pdf/2007/GL03_ST7(R).pdf)) and *VICH-GL-8 Stability Testing for Medicated Premixes* (http://www.vichsec.org/pdf/2000/GL08_ST7.pdf).

Annexe 1

Glossary of Terms

The following definitions are provided to complement those already available under the Glossary of Terms of the GMP Guidelines (GUI-0001).

Drug Premix - 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*).

Dilute Drug Premix - 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. (Section C.01A.001 of the *Food and Drug Regulations*)

Feed Ingredient - Any substance or mixture of substance that is assessed or evaluated as being acceptable for use in feeds.

Medicated Feed - A mixed feed that contains a medicating ingredient [2.(1) of the *Feeds Regulations*, 1983]

Withdrawal Period - The length of time between the last administration of a drug to an animal and the time when tissues or products collected from the treated animal for consumption as food contain a level of residue of the drug that would not likely cause injury to human health. (Section C.01.001 of the *Food and Drug Regulations*)