Health Canada Santé Canada

Our mandate:

To manage and deliver a national compliance and enforcement program for blood and donor semen; cells, tissues and organs; drugs (human and veterinary); medical devices and natural health products, collaborating with and across, all regions.

Health Products and Food Branch Inspectorate

Standard for the Fabrication, Control and Distribution of Antimicrobial Agents for Use on Environmental Surfaces and Certain Medical Devices (GUI-0049)

Supersedes:
2004-12-01

Date issued:
2012-09-25

Date of implementation:
2012-09-25

Ce document est aussi disponible en français.

Canada

Table of Contents

Introduction

Antimicrobial agents for use on environmental surfaces and certain medical devices have been exempted from the requirements of Division 1A (Establishment Licences) and Division 2 (Good Manufacturing Practices (GMP)) of Part C of the *Food and Drug Regulations*. However, all other pertinent requirements of the *Food and Drugs Act* and Regulations still apply. This standard is considered a voluntary standard and is considered an acceptable means to meet, among others, the requirements of Section 8 of the *Food and Drugs Act* addressing manufacturing under sanitary conditions.

Since this standard does not meet the World Health Organization (WHO) requirements for the manufacture of pharmaceutical products, Certificates of Pharmaceutical Product (CPP) will not be issued by Health Canada for products manufactured according to this standard.

In addition, products manufactured according to this standard are not covered by the scope of the Mutual Recognition Agreements (MRA) as this standard is not equivalent to the current Canadian GMP guidelines.

A. General

1. Scope

1.1 This standard applies to fabricators, packagers/labellers, distributors, testers and importers of any antimicrobial agents for use on environmental surfaces and medical devices that are not invasive devices as defined in the *Medical Devices Regulations* and are intended to come into contact with intact skin only.

1.2 This standard does not apply to the following products as they are still subject to the current GMP regulations and guidelines:

a) antimicrobial agents used for contact lenses which are required to be sterile,

b) chemosterilants and high level antimicrobial agents used to sterilize invasive devices or devices used for circulation and reintroduction of a body fluid,

c) any other antimicrobial agents used for devices to be introduced in a body cavity or that come in contact with a body fluid.

2. Glossary

Anti-microbial Agent – “means a drug that is capable of destroying pathogenic micro-organisms and that is labelled as being for use in the disinfection of environmental surfaces or certain medical devices, as defined in the Medical Devices Regulations, that

(a) are not invasive devices as defined in those Regulations; and
(b) are intended to come into contact with intact skin only.”

Batch - A quantity of drug in dosage form, a raw material, or a packaging material, homogeneous within specified limits, produced according to a single production order and as attested by the signatories to the order. In the case of continuous manufacture, a batch corresponds to a defined fraction of the production, that is characterized by its intended homogeneity. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch.

Bulk antimicrobial agent - Unpackaged final product, usually in quantities larger than the largest commercially available package size.

Distributor or Manufacturer – “A person, including an association or partnership, who under their own name, or under a trade, design or word mark, trade name or other name, word, or mark controlled by them, sells a food or drug.”

Environmental surface - Floors, walls, ceilings, and other surfaces where extraneous material can collect.

Fabricate – “To prepare and preserve a drug for the purpose of sale.”

Finished Product - A product that has undergone all stages of production, including packaging in its final container and labelling.

Import – “To import into Canada a drug for the purpose of sale.”

In-Process Antimicrobial Agent - Product in a semi-finished form, or in a form other than its final form.

In-process Drug - Any material or mixture of materials that must, to become a drug in dosage form, undergo further processing.

Invasive Device – “means a medical device that is intended to come into contact with the surface of the eye or penetrate the body, either through a body orifice or through the body surface.”

Lot - A quantity of any drug in dosage form, a raw material, or a packaging material, homogeneous within specific limits, constituting all or part of a single batch and identified by a distinctive lot number that appears on the label of the finished product.

Lot Number – “means any combination of letters, figures, or both, by which any food or drug can be traced in manufacture and identified in distribution.”

Master Formula - A document or set of documents specifying the raw materials with their quantities and the packaging materials, together with a detailed description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls.

Packaging Material - Labels, printed packaging materials and those components in direct contact with the dosage form.

Quarantine - Effective restriction of the availability of material or product for use (physically or by system), until released by the quality control department.

Raw Material - Any substance, other than in-process drug or packaging material, intended to be used in the manufacture of drugs, including those that appear in the master formula but that do not appear in the drug such as solvents and processing aids.

Specification – “Means a detailed description of a drug, the raw material used in a drug, or the packaging material for a drug and includes:

> (a) a statement of all properties and qualities of the drug, raw material or packaging material that are relevant to the manufacture, packaging, and use of the drug, including the identity, potency, and purity of the drug, raw material, or packaging material,
> (b) a detailed description of the methods used for testing and examining the drug, raw material, or packaging material, and
> (c) a statement of tolerances for the properties and qualities of the drug, raw material, or packaging material.”

B. Standard

1. Premises

1.1 All processing and packaging areas shall be of material, construction, and finish that will permit the ready and efficient cleaning. Uncleanable surfaces are kept to a minimum.

1.2 Premises are designed, constructed and maintained to prevent the introduction or migration of extraneous materials, insects or other animals into antimicrobial agents.

1.3 Drains shall be of adequate size and suitable type, and where connected directly to a sewer, they shall be equipped with traps or alternative device.

1.4 Adequate light and ventilation shall be provided in all working areas.

1.5 Rest, change, wash-up and toilet facilities are separated from production areas.

1.6 Premises shall have systems in place for appropriate quarantine. Where electronic quarantine is used, electronic access is restricted to authorized personnel.

2. Equipment

2.1 All processing, packaging, and testing equipment shall be:

2.1.1 Designed and located so as to permit ready and thorough cleaning, and made of materials and construction that will not contaminate or add extraneous materials to antimicrobial agents for which it is used. Maintained in a good state of repair when in use.

2.1.2 Maintained to serve its intended purpose and to prevent contamination of the antimicrobial agent with extraneous materials: scales and other measuring equipment used in production and control are calibrated on a scheduled basis. As well, automated, mechanical, electronic or any other types of equipment used in production are checked/calibrated at defined intervals, and records are kept.

3. Personnel

3.1 Qualified Personnel - Technically qualified personnel shall be:

3.1.1 For fabricators, individuals in charge of Manufacturing and Quality Control have graduated from a university of recognized standing, with a science degree or have appropriate combination of scientific and technical qualifications, with at least 2 years of relevant practical experience in the formulation or testing of antimicrobial agents or other types of drugs. They can delegate their duties to persons with proper training and experience.

3.1.2 Individuals responsible for packaging operations, including control over printed packaging materials and withdrawal of bulk substances are persons qualified by training and experience.

3.1.3 For distributors and importers, the individual responsible for Quality Control is qualified by training or experience.

3.2 Maintenance Personnel - Personnel in charge of all equipment and machinery shall be suitably qualified.

4. Sanitation

4.1 A written sanitation program shall be available and implemented for fabricators and packagers/labellers.

4.2 The sanitation program contains procedures that should keep the premises clean, sanitary, orderly and free from waste, debris, vermin and pests. As a minimum, it should include:

4.2.1 Cleaning requirements applicable to all production areas and processing equipment;

4.2.2 Cleaning intervals;

4.2.3 Responsibility for implementation of the program, including outside contractor's responsibilities, if applicable;

4.2.4 Disposal procedures for waste material and debris;

4.2.5 Pest control measures;

4.2.6 Precautions required to prevent contamination of antimicrobial agent with rodenticides, insecticides and fumigation agents;

4.3 Toilet and washup facilities and sanitary supplies shall be provided and maintained in satisfactory condition at all times.

4.4 Unsanitary practices, such as smoking, eating and drinking shall not be permitted in fabrication and packaging/labelling areas.

5. Raw Material and Packaging Material Testing

5.1 Each raw material shall be covered by detailed written specifications as defined under “Specifications” in the Glossary.

5.2 Each lot or batch of raw material is accompanied by a Certificate of Analysis showing actual numerical results, with reference to the specifications, issued by the raw material fabricator. If the Certificate of Analysis is not available from the fabricator, each lot of raw material must be quarantined, sampled after receipt on the premises and tested to ensure compliance with the applicable specifications; all analytical results shall be recorded.

5.3 The use of each lot of active raw material must be approved by a responsible person of the Quality Control. This approval is documented or recorded electronically.

5.4 The disposal of all rejected material is documented or recorded electronically.

5.5 Labels and other packaging material shall be covered by detailed written specifications as defined under “Specifications” in the Glossary.

5.6 Each lot or batch of packaging material is examined prior to use to ensure compliance with the applicable specifications and such examination and / or testing is documented, or recorded electronically.

5.7 The records for all raw materials and packaging materials released for manufacture shall be reviewed by a responsible person and filed.

6. Manufacturing Control

6.1 Raw materials and Packaging Materials - Upon receipt, all bulk and in-process antimicrobial agents and all raw materials and packaging materials used in processing shall be:

6.1.1 Identified by a lot number, receiving number or laboratory control number, and fully accounted for by records.

6.1.2 Generally kept in an area separate from immediate manufacturing areas.

6.1.3 Stored in such a way as to preserve potency and quality.

6.1.4 Adequately labelled as to identity.

6.2 Manufacturing Operations

6.2.1 When applicable all raw materials for processing are dispensed and verified by a process control system and weighed in clean and properly labelled containers as to identity and quantity. Where possible, the weighed materials should be grouped for each batch.

6.2.2 Before any manufacturing and packaging operation is started, steps are taken to ensure that the work area and equipment are clean and free from any raw materials, products, product residues, labels or documents not required for the current operation.

6.2.3 Batches or lots of finished products shall only be combined when there is appropriate testing of the combined lots as described in Section B.10 (Finished product testing).

6.2.4 Processing operations are covered by a Master Formula, which is prepared by, and is subject to independent checks by personnel complying with paragraph 3.1.1.

6.2.5 The Master Formula is written to provide not less than 100 % of the label claim. The Master Formula should also include the following information:

- the name of the product, strength and batch size or the volumetric or gravimetric process rate for continuous processing;
- a list of all raw materials to be used with the amount of each to be used;
- the principal equipment to be used and any in-process controls;
- checks on materials, pretreatments, sequence for adding materials, mixing times, temperatures with their limits;
- where necessary, the requirements for storage of the products and any special storage conditions;
- any special precautions to be observed;
- for a packaged product, a complete list of all the packaging materials in direct contact with the product required for a standard batch size, including the code or reference number relating to the specifications for each of these packaging materials.

6.2.6 Each batch or lot processed shall be governed by an individually numbered manufacturing order issued by personnel complying with paragraph 3.1.1, except for continuous production systems.

6.2.7 As it becomes available during the process, the following information is included on or attached to the manufacturing order or otherwise made part of the manufacturing records:

- the name of the product and the batch or lot number;
- dates of start and completion (dates of manufacture);
- for the active raw material, the lot or batch number and the quantity of each raw material actually weighed and dispensed. This quantity is to be adjusted to the assay result of the active raw material ONLY when it is less than 97 % ;
- if appropriate, the results of the required in-process checks;

- any deviation from instructions with a report of investigation.

6.3 Packaging

6.3.1 Printed packaging materials and labels shall be:

6.3.1.1 Withdrawn against a manufacturing / production order.

6.3.1.2 Issued and checked by personnel complying with paragraph 3.1.2.

6.3.2 The packaging and labelling processes shall be supervised by personnel complying with paragraph 3.1.2.

6.3.3 All packaging operations shall be performed following the issue of packaging orders.

6.3.4 All packaging operations shall be performed according to comprehensive and detailed written operating procedures or specifications, which shall include procedures for unused printed packaging materials.

6.3.5 The following information shall be recorded:

- the name of the product, batch number and quantity of bulk to be packaged;
- quantity and reference number of printed materials and bulk products issued, used, destroyed and returned to stock.

6.3.6 Every package of antimicrobial agent shall be identified by a lot number.

6.3.7 All packaged antimicrobial agents shall be held in quarantine and so identified until released by Quality Control.

6.3.8 Packaged antimicrobial agents shall be stored and transported under conditions specified by Quality Control to preserve their potency, quality and safety.

7. Quality Control

7.1 A fabricator, packager/labeller, distributor and importer shall have a person responsible for Quality Control as described under paragraph 3.

7.2 For a fabricator or a packager/labeller, the Quality Control shall have:

7.2.1 Assigned and adequately trained personnel.

7.2.2 A Control Laboratory, or have true and effective access to adequate equipment and facilities for inspecting and testing, to ensure the quality, identity, potency, purity and safety of all ingredients and materials used in the production of antimicrobial agents.

7.3 The Quality Control is also responsible for:

7.3.1 Establishing Standard Operating Procedures (SOPs) for the sampling to be carried out.

7.3.2 Approving applicable specifications and quality control procedures unless this task was performed by a research and development person.

7.3.3 Checking to see that all processing, packaging and storage specifications are met.

7.3.4 The review of all documentation, including manufacturing and packaging orders to ensure that all specifications and limits have been met.

7.3.5 Checking to see that disposal procedures for rejected materials are followed.

7.3.6 Maintaining Quality Control records.

8. Self-Inspection Program

Fabricators and packagers/labellers shall have a self-inspection program to ensure compliance with this standard. A comprehensive written procedure shall be available describing the functions of the self-inspection program. The program shall include as a minimum:

a) Periodic self-inspection;

b) Written reports of the findings of these inspections;

c) Written reports of the necessary corrective action taken.

9. Recall

A distributor or importer who sells an antimicrobial agent shall maintain a system of control to permit the complete and rapid recall of any lot or batch of the antimicrobial agent on the market.

10. Finished Product Testing

10.1 All finished products shall be covered by detailed written specifications as defined under “Specifications” in the Glossary.

10.2 Each batch or lot of antimicrobial agent in finished form shall be tested to ensure compliance with its specifications prior to its availability for sale.

10.3 No lot or batch of antimicrobial agent shall be made available for sale unless it complies with its specifications.

10.4 Records of these tests shall be in a lucid form and shall state the actual results of the tests, the methods used, identity of testing laboratory, signature and name of a responsible person of that laboratory, and shall be signed and dated by the person responsible for the Quality Control.

11. Records

11.1 Every fabricator, packager/labeller, distributor and importer shall maintain the following documentation on their premises in Canada:

11.1.1 The Master Formula.

11.1.2 Evidence that each batch or lot is manufactured according to the Master Formula

11.1.3 Evidence that the conditions under which the antimicrobial agent is fabricated, packaged/labelled, tested and stored are in compliance with this standard or an ISO standard.

11.1.4 Evidence establishing the shelf-life of the antimicrobial agent.

11.1.5 Evidence of testing as referred to in Section 10.

11.1.6 Records of sales in a manner sufficient to recall an antimicrobial agent from the market

11.1.7 Records of any complaint and of its investigation.

The above documentation should be available within 48 hours for activities carried out by third parties.

11.2 Every fabricator and packager/labeller shall maintain on their premises in Canada:

11.2.1 The written specifications of the raw material/packaging material.

11.2.2 Evidence that the materials have been tested/examined according to these specifications.

11.2.3 On request, the distributor and importer shall make available the results of testing/examination performed on any lot of those materials used to fabricate a lot or batch of an antimicrobial agent.

The above documentation should be available within 48 hours for activities carried out by third parties.

11.3 Period of retention

11.3.1 Records and evidence on the fabrication, packaging/labelling, testing and storage of an antimicrobial agent are required to be maintained for at least two years from the date of the manufacture.

11.3.2 Records and evidence on the testing/examination of raw materials and packaging materials shall be maintained for a period of one year after the materials were last used.

12. Stability

Data shall be developed and recorded to determine the stability of the formulation.

13. Complaints and Returned Products

A fabricator, packager / labeller, distributor and importer shall have a procedure for handling complaints respecting quality of each antimicrobial agent distributed as well as any returned product.