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December 28, 2001

01-118727-970

To: Associations

Following the publication, on July 30, 2001, of the draft version of the **Standard for the Fabrication, Control and Distribution of Antimicrobial Agents for Use on Environmental Surfaces and Non-Critical Medical Devices**, comments were received to the effect that certain sections of this standard did not described with enough details the required information. Specifically, the "Records" section has been expanded to describe with more details the records and evidence to be maintained by a fabricator, packager/labeller, distributor or importer of antimicrobial agents.

Given that these changes are deemed significant, this document is re-published as a draft on the Web site of the Health Products and Food Branch Inspectorate at the following address:

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

As already indicated, please note that this proposed standard does not meet the World Health Organization (WHO) standard for the manufacture of pharmaceutical products. Consequently, WHO certificates for exportation cannot and will not be issued for those products.

Comments on this document should be submitted to Ms. France Dansereau, Head of the Inspection Unit, National Coordination Centre, Health Products and Food Branch Inspectorate **no later than February 28, 2002,** by e-mail at france_dansereau@hc-sc.gc.ca or by fax at (613) 952-9805.

Yours truly,

Original signed by
Heather Sutcliffe (for)

Jean Lambert
Director General

Health Canada
Health Products and Food Branch

OUR MANDATE:

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

STANDARD
FOR THE FABRICATION, CONTROL AND DISTRIBUTION OF ANTIMICROBIAL AGENTS FOR USE ON ENVIRONMENTAL SURFACES AND NON-CRITICAL MEDICAL DEVICES

Supersedes	Draft issued July 1st, 2001
Date issued	December 1st 2001
Date of implementation	Draft for comments

Ce document est aussi disponible en français.

Canada

A. GENERAL

1. SCOPE

1.1 This standard applies to the fabrication, control and distribution of any antimicrobial agents for use on environmental surfaces and non-critical medical devices.

1.2 This standard does not apply to:

a) disinfectants used for contact lens which are required to be sterile,

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

c) any other disinfectants used for devices to be introduced in a body cavity.

The above products will continue to be subject to current Good Manufacturing Practices Guidelines and Regulations.

1.3 This standard applies to fabricators, packagers/labellers, distributors and importers of antimicrobial agents.

2. GLOSSARY

2. 1 SPECIFICATION - A description of each material or substance (raw material or finish product) which includes definitions of all properties and qualities including identity, purity, and potency that are relevant to the manufacture and use of the disinfectants and sanitizers, together with tolerances and a description of all tests or analyses used to determine those properties and qualities, in sufficient detail to permit performance by suitable qualified personnel.

2.1.1 CRITICAL SPECIFICATION: means specifications that are related to the efficacy and performance of the product (such as potency).

2.1.2 NON-CRITICAL SPECIFICATION: means specification that are not integral to the efficacy or performance of a product.

2. 2 BATCH - A quantity of any antimicrobial agent, homogeneous within specified limits, manufactured according to a single manufacturing order.

2. 3 BULK Antimicrobial agent - Unpackaged final product, usually in quantities larger than the largest commercially available package size.

2. 4 Antimicrobial agent - for the purpose of this document the term antimicrobial agent is used for disinfectant and sanitizer products for use on environmental surfaces and non-critical medical devices to control a human or animal pathogen. This term includes the following

types of products and claims:

2.4.1 Antimicrobial Agents with DIN - Substances represented for use

a) on environmental surfaces and other inanimate objects, for the mitigation or prevention of disease in humans or animals:

i) in facilities and premises where food is manufactured, prepared or stored; or
ii) in patient care areas of health care facilities, such as hospitals, nursing homes, and medical, dental and veterinary clinics; or
iii) in and around the home or commercial or public premises.

b) as disinfectants or for use on environmental surfaces and non-critical medical devices.

2.4.2 Disinfectant - An antimicrobial agent capable of destroying pathogenic and potentially pathogenic micro-organisms on inanimate surfaces. A disinfectant without specified target organisms on the container label is regarded only as a bactericide.

2.4.3 High-level Disinfectant - An antimicrobial agent that kills all microbial pathogens, except large numbers of bacterial endospores, when used in accordance with labelling.

2.4.4 Low level Disinfectant - An antimicrobial agent that kills most vegetative bacteria and lipid or medium-sized viruses.

2.4.5 Chemosterilant - An antimicrobial agent capable of destroying all forms of micro-organisms (including bacterial spores) on inanimate surfaces.

2.4.6 Sporicide - An antimicrobial agent capable of destroying bacterial spores.

2.4.7 Virucide - An antimicrobial agent capable of destroying viruses.

2.4.8 Bactericide - An antimicrobial agent capable of destroying bacteria, but not necessarily bacterial spores or mycobacteria.

2.4.9 Germicide - Synonymous with disinfectant.

2.4.10 Fungicide - An antimicrobial agent capable of destroying fungi, including their spores.

2.4.11 Tuberculocide - An antimicrobial agent capable of destroying mycobacteria.

2.4.12 Mycobactericide - Synonymous with tuberculocide.

2.4.13 Sanitizers - Products that reduce the level of micro-organisms present by significant numbers, i.e., 99.9% or more, or to acceptable levels established by federal or

provincial health authorities.

2. 5 FINISHED PRODUCT - An antimicrobial agent in its final form.

2. 6 IN-PROCESS Antimicrobial agent - Material in a semi-finished form, or material other than its final form.

2. 7 LOT - A quantity of any antimicrobial agent, homogeneous within specified limits, constituting all or part of a single batch, and identified by a distinctive lot number.

2. 8 LOT NUMBER - Any combination of letters, figures, or both, by which any antimicrobial agent can be traced in manufacture and identified in distribution.

2. 9 PACKAGING MATERIAL - Labels, and those components in direct contact with the finished product.

2.10 QUARANTINE - Status of material stored separately and not available for use until released by a designated authority.

2.11 RAW MATERIAL - Any substance intended to be used in the manufacture of a antimicrobial agent in finished form.

2.12 Non-critical Medical Device: any devices that is not:

- an invasive device;
- a device through which a body fluid is circulated and reintroduced in the body;
- a device to be introduced in a body cavity.

3. APPLICABLE ACTS AND REGULATIONS

(This Section will be updated as required based on changes to the regulatory framework)

In addition to complying with this standard, the manufacture, testing, and handling of all antimicrobial agents shall conform to the relevant provisions of the following:

3.1 Food and Drugs Act and Regulations.

~~3.2 Can / CGSB - 2.161-97 Assessment of efficacy of antimicrobial agents for use on environmental surfaces and medical devices.~~

B. SPECIFICATIONS

1. PREMISES

1.1 All processing, packaging and testing areas shall be of material, construction, and finish that will permit the ready and efficient cleaning: surfaces are smooth and non-porous, joints are sealed, 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 others animals into antimicrobial agent products.

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 waste disposal systems.

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

1.5 Rest, change, wash-up and toilets facilities, when possible, are well separated from production areas.

1.6 Where physical quarantine areas are used, they are well marked with access restricted to authorized personnel. 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 and packagers/labellers, individuals in charge of Manufacturing and Quality Control are graduated from a university of recognized standing, with a science degree or has appropriate combination of scientific and technical qualifications, with at least 2 years of practical experience in the formulation, processing, packaging, labelling, and testing of antimicrobial agents.

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 and are directly responsible to the person in charge of the manufacturing department or a person having the same qualifications.

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 and shall be responsible to a person complying with the requirements of paragraph 3.1.1.

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 pest. 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 Outside contractor's responsibilities;

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 No unsanitary practices, such as smoking, eating and drinking shall be permitted in fabrication and packaging / labelling areas.

5. RAW MATERIAL AND PACKAGING MATERIAL TESTING

5.1 Each raw material and unprinted packaging material shall be :

5.1.1 Covered by detailed written specifications as defined under “specification” in the Glossary.

5.1.2 Each lot or batch is accompanied by a Certificate of Analysis showing actual numerical results, with reference to the specifications, issued by the raw materials 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 reports shall be recorded and those covering active ingredients shall be signed and dated by a responsible person of the Quality Control. Materials not meeting their specifications

may exceptionally be used in production if it is demonstrated that the quality of the finished product will not be altered and if proper adjustment to the formulation is made.

5.1.3 The records available shall be in a lucid form, state results of tests, make reference to methods used, indicate the identity of testing laboratory, contain the signature and name of a responsible person of that laboratory, and include disposal of rejected raw material.

5.2 Each labels and printed packaging material shall be :

5.2.1 Covered by detailed written specifications as defined under “Specifications” in the Glossary.

5.2.2 Each lot or batch is examined prior to use to ensure compliance with the applicable specifications.

5.2.3 Supported by records signed by a responsible person as described under 3.1.2. in Personnel to demonstrate that such examination and / or testing has been performed. The records shall include disposal of rejected lots.

5.3 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 and documented 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 At all times during processing, all materials, in-process or fully processed bulk containers, major equipment, and the rooms used are identified for the product or material being processed, its strength and the batch or lot number. Automated controls can be used.

6.2.4 Batches or lots are combined only with the approval of the Quality Control. Records are kept.

6.2.5 Processing operations are covered by Master Production Documents, which are prepared by, and are subject to independent checks by personnel complying with paragraph 3.1.1.

6.2.6 The Master Production Documents should include a Master Formula written to provide not less than 100% of the label claim. Adjustment is permitted in the quantity of the active material if the assay value is less than 97%. 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.

6.2.7 Each batch or lot processed shall be governed by an individually numbered manufacturing order issued by personnel complying with paragraph 3.1.1.

6.2.8 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 (adjusted where necessary according to assay results) actually weighed and dispensed;
- 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 manufacturing / 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 Quality Control person as described under paragraph 3, on the premises, responsible for that activity, reporting to Management.

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

7.2.1 Personnel and functions separate and distinct from Manufacturing and Sales Department.

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 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 The complaint handling procedure respecting quality on each finished antimicrobial agent distributed, during or after its distribution and record keeping. (applies to all establishments)

7.3.6 The inspection and disposition of all returned products. (applies to all establishments)

7.3.7 Checking to see that disposal procedures for rejected materials are followed. (applies to all establishments)

7.3.8 Maintaining Quality Control records in a lucid form.

8. SELF-INSPECTION PROGRAM

Fabricators and packagers / labellers shall establish a self-inspection program, having regard for its suitability to the operation, to ensure the development and implementation of the highest standards of quality management. 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 manufacturer who sells a 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, prior to its availability on sale, tested to ensure compliance with the critical specifications.

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

10.4 Records of these tests shall be in a lucid form and shall state the actual result of the tests, the methods used, identity of testing laboratory, and 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 of the antimicrobial agent

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 the 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.

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.

11.3 Period of retention

11.3.1 Records and evidence on the fabrication, packaging / labelling, testing and storage of an antimicrobial agent that are required to be maintained according to this standard must be retained to the earlier of three years from the date of the manufacture of the antimicrobial agent or one year after the expiration date on the label.

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

12. SAMPLES

12.1 Samples of all raw materials shall be retained by the fabricator for a period of two years after the date of their last use in a finished product.

12.2 A sample of each batch of the finished antimicrobial agent shall be kept in Canada by the company under suitable conditions of storage until the expiration of five years from the date of the testing of the antimicrobial agent, or the expiration date of the antimicrobial agent, plus one year. Such samples shall be maintained in the retail package where practicable, or in containers of similar material and construction. A manufacturer who sells a antimicrobial agent shall submit to the Director upon request an adequate portion of the product. The sample size should be sufficient to perform at least twice all required tests.

13. STABILITY

Product stability shall be determined prior to marketing and prior to adoption of significant formulation or packaging changes. Data shall be developed and recorded to determine the stability of the formulation. For new chemical entities, three lots shall be sampled for the development of shelf-life data. For existing chemical entities, data obtained from two lots are deemed sufficient.