Health Canada Santé Canada

GUIDANCE DOCUMENT

Safety and Effectiveness Requirements for High-Level Disinfectants and Sterilants for use on Reusable Semi-Critical and Critical Medical Devices (2018)

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Health Products and Food Branch

Canada

Our mission is to help the people of Canada maintain and improve their health. *Health Canada*	The Health Products and Food Branch's mandate is to take an integrated approach to the management of the risks and benefits to health related products and food by: • minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food; and • promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health. *Health Products and Food Branch*

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FOREWORD

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada mandates and objectives should be implemented in a manner that is fair, consistent and effective.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document ***may be*** acceptable provided they are supported by adequate justification. Alternate approaches should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, in order to allow the Department to adequately assess the safety, efficacy or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable guidance documents.

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1. INTRODUCTION

This guidance document outlines the information considered necessary to support the safety and effectiveness of chemical products that are represented for use as high-level disinfectants and sterilants on reusable semi-critical and critical medical devices, which are regulated as medical devices under the *Medical Devices Regulations.*

The safety and effectiveness requirements specific to contact lens disinfectants are addressed in a separate guidance document:

- Safety and Effectiveness Requirements for Contact Lens Disinfectants (2018)

1.1 Policy Objectives

The objective of this guidance document is to provide applicants of high-level disinfectants and sterilants the necessary information to comply with the *Medical Devices Regulations.*

1.2 Policy Statements

Applicants must provide Health Canada with sufficient information to support the safety, effectiveness and quality of a disinfectant device when used in accordance with the label's recommended conditions of use before market authorization can be granted.

Health Canada must evaluate this information and determine whether a medical device licence should be issued.

1.3 Scope and Application

This guidance document applies to products regulated as medical devices under the *Medical Devices Regulations* that are represented for use as:

- high-level disinfectants and sterilants for use on reusable semi-critical and critical medical devices.

All high-level disinfectants and sterilants for use on reusable semi-critical and critical devices must also meet the labelling requirements set out by the *Medical Devices Regulations.*

2. GUIDANCE FOR IMPLEMENTATION

The effectiveness and safety requirements in this guidance document are not exhaustive and other appropriately validated test methods and protocols may be acceptable (e.g., those published by standards organizations or recommended by other international regulators). As the

requirements and protocols within this guidance document are modelled on those recommended by the United States Food and Drug Administration (U.S. FDA), applicants are encouraged to additionally reference the U.S. FDA premarket notification 510(k) submission documents:

- *Guidance for Industry and FDA Reviewers: Content and Format of Premarket Notification [510(k)] Submissions for Liquid Chemical Sterilants/High Level Disinfectants*.
- *Guidance on Premarket Notification [510(k)] Submissions for Sterilizers Intended for Use in Health Care Facilities*

Applicants are encouraged to contact Health Canada in advance of submitting an application to determine the specific data requirements that may be considered necessary.

2.1 Overview of Effectiveness Requirements

A three-tiered testing regime is recommended by Health Canada to support the effectiveness of high-level disinfectants and sterilants represented for use on reusable semi-critical and critical medical devices, which includes:

a) **Potency Tests**: These are conducted to demonstrate the potential for a product to be used as a high-level disinfectant or sterilant, by establishing a broad spectrum of microbicidal activity for the test product.
   - Effectiveness testing to demonstrate that the product is a sporicide, mycobactericide, virucide, fungicide and bactericide is required.

b) **Simulated-Use Tests (tests of inoculated instruments)**: These are conducted to verify the effectiveness of a product when used in accordance with the label's recommended conditions of use, and they help identify conditions under which the product may fail.
   - Effectiveness testing is conducted in controlled laboratory tests in which representative medical devices are experimentally contaminated with a precise amount of microbial inoculum, then treated (i.e., cleaned and disinfected or sterilized) and tested for organism recovery.

c) **In-Use Tests (tests of clinically-used instruments)**: These are conducted to confirm the results of simulated-use testing and to estimate the actual effectiveness outcomes during clinical use, given that unforeseen factors may impact the effectiveness of a product and limit the correlation of the potency and simulated-use tests to actual use conditions.
   - Effectiveness is conducted in a clinical setting using devices that are processed by facility personnel who have been instructed to reprocess the representative devices (i.e., clean and disinfect or sterilize) according to the device's labelling.

Specific information on how to conduct these different types of tests, and the associated performance criteria that must be met for the tests to be valid, is provided in Sections 2.2 and 2.3.

2.1.1 Effectiveness Considerations for High Level Disinfectants and Sterilants

2.1.1.1 Good Laboratory Practice

Efficacy testing should be conducted in accordance with Good Laboratory Practice (GLP) principles endorsed by Health Canada to ensure that the data is of high quality and reliable. Acceptable standards include those published by the Organisation for Economic Co-Operation and Development (OECD), and the United States Environmental Protection Agency (U.S. EPA), and the United States Food and Drug Administration (U.S. FDA). Applicants should reference the following guidance document for information on providing evidence to Health Canada that efficacy studies adhere to the principles of Good Laboratory Practice:

- *Guidance Document Non-Clinical Laboratory Study Data Supporting Drug Product Applications and Submissions: Adherence to Good Laboratory Practice*

2.1.1.2 Efficacy Data Reporting

Efficacy data submitted should be presented in a report format, and should include the following information:

- The identification of the testing laboratory or organization (i.e., the name and address) and the dates on which the study was initiated and completed, terminated or discontinued;
- A statement of Good Laboratory Practice (GLP) compliance;
- The test method used, and any deviations or modifications made to the standard test parameters or methodologies;
- For alternate test methods not expressly recommended by Health Canada (i.e., for in-use testing or simulated-use testing), complete testing protocols should be submitted, including an overview of the materials and procedures employed in testing;
- The test organisms used, including identification of the specific strain and stock supplier (e.g., the American Type Culture Collection identifier);
- The product name or identification number, and the number of batches tested;
- The concentration of the active ingredient(s) for each batch tested, and if any were aged or stressed, for how long and under what conditions;
- For products that are diluted from a concentrated formulation, how the dilution was prepared;
- The level of water hardness used in the test, if the test product was diluted;
- The type and level of soil load used in the test;
- The initial inoculums of the test organisms;
- The number and type of carriers or replicates used in the test;

- The identification of all material or procedural options employed, where such choice is provided for or recommended in the test method selected (e.g., growth media, drying time for inoculated carriers, neutralization confirmation and/or subculture media, secondary sub-culturing);
- The test exposure conditions used in the test (i.e., contact time, temperature, and relative humidity);
- The inoculum counts or carrier counts required to validate the test;
- Any control data essential to establish the validity of the test;
- An overview of the statistical plan and assumptions for analyzing the data;
- The raw data obtained, in tabular form (i.e., the numerical test results obtained through the study should be submitted for assessment; the submission of test summaries alone is not considered acceptable) and;
- A conclusion, describing whether the product meets the specific performance criteria relative to the test method(s) employed.

2.1.1.3 Batch Replication Requirement

It is expected that if a product can demonstrate effectiveness as both a sporicide and mycobactericide that less-resistant microorganisms will also be effectively destroyed or inactivated by the product; therefore, once the sporicide and mycobactericide claims have been established to support the potency testing requirements, testing against only 1 sample of the test product per microorganism is acceptable to support all virus, fungi and bacteria claims (general and/or specific claims). The batch tested should be one of the three used in the sporicidal effectiveness testing for the proposed product.

2.1.1.4 Addition of Activator

Products that are intended to have an activator added prior to their use should be tested using batches of the test product which have been activated as specified in their directions for use.

2.1.1.5 Temperature

The temperature used during the course of efficacy testing (e.g., during the inoculation of carriers, exposure of carriers to the test substance, and during neutralization confirmation), should be according to the labelled directions for use. A default temperature of 18-25^{o}C should be used unless the label of the test product specifies otherwise.

2.1.1.6 Neutralization

Neutralization procedures should be employed at the completion of the contact time for all efficacy tests in order to preclude residual effects of the active ingredients in the subculture medium. Health Canada recommends the ASTM E1054 method be used to validate the neutralizers used for disinfectant tests for all microorganisms except for viruses. For virucidal tests, the ASTM E1482 method should be used.

2.1.1.7 Testing of Product under "Worst Case" Conditions

All effectiveness testing should be conducted under "worst-case" conditions in order to establish that the product will remain effective for the duration of the shelf life (i.e., using batches which have been formulated at or below the lower active ingredient limit or lower certified limit and aged or stressed to the limit of the product's proposed shelf life). Additionally, testing should be conducted in accordance with the labelled recommendations for use (e.g., contact time, organic burden, temperature stressed to the end of its claimed reuse life).

In the absence of real-time aged samples of the test product, effectiveness testing using at least one accelerated batch of the product (i.e., where the product is stored at an elevated temperature and relative humidity for a defined number of days) is acceptable to estimate the effectiveness of the product at the end of the shelf life. In general, effectiveness testing conducted with an accelerated batch which is at least 60 days old is considered to estimate a 1-year shelf-life stability.

2.1.1.8 Products Claiming Reuse Applications

Products claiming reuse applications (e.g., products for use in immersion baths) should undergo a simulated stressing or re-use procedure prior to performing effectiveness tests. An acceptable protocol should incorporate an appropriate level of organic and inorganic soil (e.g., blood, protein, salts), and should test the minimum effective concentration (MEC) of the product (i.e., the minimum concentration as determined by dose response testing required to achieve the claimed effectiveness of the product).

2.1.1.9 Testing Sterilants for Use in a Chemiclave Sterilizer

The effectiveness testing of a sterilant which is a gas/vapour/plasma (e.g., hydrogen peroxide gas plasma, ethylene oxide) and is recommended for use in a specific device (i.e., a chemiclave sterilizer) should be conducted under conditions that are consistent with the use of the product as labelled (i.e., inoculated carriers should be exposed to the recommended chemiclave cycle). The submission of test data generated using the sterilant alone (i.e., in the absence of the chemiclave) is considered insufficient.

It is recommended that applicants provide the labelling for the sterilizer device itself to Health Canada as part of their application; this labelling is expected to describe the intended use of the device, its operating characteristics and limitations, and detailed operating instructions (e.g., the specification of the cycle parameters such as temperature, time, and pressure).

2.1.1.10 Generation of Survivor Curve and Calculation of D-Value

Applicants may choose to develop a survivor curve (i.e., a graphic representation of microbial death rate kinetics for a specific product on a defined microbial population) and calculate the D-value (i.e., the log death time, or time required at a given temperature for the number of microorganisms to decrease by 1 log cycle) for their product as a measure to describe the predicted effectiveness of their product. Health Canada does not require this information to be submitted for applications in support of high-level disinfectants and sterilants for use on reusable semi-critical and critical medical devices.

2.2 Potency Testing

The information in this section provides applicants with the effectiveness data requirements considered necessary to demonstrate the potential for products to be used as high-level disinfectants and sterilants for use on reusable semi-critical and critical medical devices.

Applicants are reminded that effectiveness testing should be conducted using the current official version of all test methods, and applicants should note that:

- The microbial counts (i.e., inoculum counts or carrier counts) prescribed in the test methods must be met for the testing to be valid. For test methods which do not prescribe this information, the microbial counts specified in the following sections must be met.
- The performance criteria prescribed in the test methods must be met to support effectiveness claims. For test methods which do not prescribe this information, the performance criteria specified in the following sections must be met.
- When microbial counts exceed the prescribed levels and the product meets the prescribed performance criteria, the testing will be considered acceptable, unless otherwise specified in the test methods.

2.2.1 Sporicide Potency Testing - Sterilant and High-level Disinfectants

This section addresses the sporicidal effectiveness requirements for a product represented for use as a sterilant or a high-level disinfectant when the test method recommended in Appendix 2 is used.

Note that there are 2 key differences between a sterilant and a high-level disinfectant:

- Performance criteria for sporicidal effectiveness:
  - A sterilant is expected to kill all bacterial spores present on a target surface (i.e., 60/60 carriers must be negative for growth in potency test).
  - A high-level disinfectant is only expected to kill a high number of bacterial spores present on a target surface (i.e, 59/60 carriers must be negative for growth in potency test).
- Contact time for sporicidal effectiveness:
  - For a sterilant, the labeled contact time must be that required to achieve the required performance criteria for sporicidal efficacy.
  - For a high-level disinfectant, sporicidal efficacy must be demonstrated in not more than 10 hours. Once the sporicidal efficacy has been demonstrated, additional potency testing must be conducted at a shorter contact time to demonstrate the mycobactericidal activity. The labeled contact time for high-level disinfection must not be less than the time required for mycobactericidal activity.

In addition to a proposed product meeting the potency requirement for the relevant sporicidal claim, confirmatory testing must be conducted for both a sterilant and a high-level disinfectant to support all of the following claims:

- Mycobactericide
- Virucide
- Fungicide
- Bactericide

2.2.1.1 Test Organisms

Effectiveness data is required against both:

- *Bacillus subtilis* (ATCC 19659)
- *Clostridium sporogenes* (ATCC 3584)

No additional bacterial spore claims are required to support the potency testing, however applicants may submit additional effectiveness evidence against any specific bacterial spore claims indicated on their product's labelling (e.g., *Clostridium difficile*).

2.2.1.2 Batch Replication Requirements and Number of Carriers or Replicates

- Testing against 3 samples of the product, representing 3 separately compounded batches per bacterial spore is required.

- All 3 batches should be formulated at or below the lower active ingredient limit or the lower certified limit, and should be aged or stressed to "worst case" conditions.
- Testing of 60 inoculated carriers for each of 2 different types of carriers, as prescribed in the current version of the AOAC 966.04 method (Method I & II), per batch per bacterial spore is recommended (i.e., 2 carrier types x 2 test microorganisms x 60 carriers/type = 240 carriers per batch sample; 3 product batches x 240 carriers/batch = a total of 720 carriers must be tested).

2.2.1.3 Required Microbial Counts and Performance Standards

- The titer of the spore suspension should be sufficiently high to achieve 1×10^6 spores per carrier, although a mean of $1 \times 10^5 - 1 \times 10^6$ spores per carrier will be considered acceptable for the test to be valid, unless otherwise prescribed in the test method.
- For sterilants: 60/60 carriers per batch per carrier type must be negative for growth at the proposed contact time for a product to be represented for use as a sterilant.
- For high level disinfectants: 59/60 carriers per batch per carrier type must be negative for growth in less than 10 hours for a product to be represented for use as a high-level disinfectant.

2.2.3 Mycobactericide Potency Testing (Confirmatory)

This section addresses potency testing requirements for the mycobactericide confirmatory requirement when the test methods recommended in Appendix 3 are used.

2.2.3.1 Levels of Effectivenss and Test Organisms

Effectiveness data is required against:

- An appropriate *Mycobacterium* species (e.g., *M. bovis* BCG).

No additional mycobacteria claims are required to support the potency testing, however applicants may submit additional effectiveness evidence against any specific mycobacteria claims indicated on their product's labelling.

2.2.3.2 Batch Replication Requirements and Number of Carriers or Replicates

- Testing against 2 samples of the product, representing 2 separately compounded batches, is required. The batches must be 2 of the 3 batches used for the sporicide test.
- Testing of 10 inoculated carriers per batch is required, except when testing is conducted using the U.S. EPA Quantitative Tuberculocidal Test Method (QTB), which requires 4 replicates per batch.

2.2.3.3 Required Microbial Counts and Performance Standards

- A minimum geometric mean of 1 x 10^6 colony forming units (CFU) per carrier is required for a valid qualitative test. The inoculum may need to be appropriately concentrated or adjusted to achieve this minimum requirement.
- For the qualitative test method, 10 of the 10 carriers tested must be negative for growth per batch at the proposed contact time, with no growth in any of the inoculated subculture media.
- For the U.S. EPA Quantitative Tuberculocidal Test Method (QTB), a minimum 99.9999% reduction is required.

2.2.4 Virucide Potency Testing

This section addresses potency testing requirements for the virucide confirmatory requirement when the test methods recommended in Appendix 4 are used.

2.2.4.1 Test Organisms

Effectiveness data is required against:

- Any virus, however Health Canada encourages testing using one of the following viruses: Poliovirus type 1, Chat strain (ATCC VR-1562) **or** Human adenovirus type 5 (ATCC VR-5 or VR-16) **or** Bovine parvovirus (ATCC VR-767) **or** Canine parvovirus (ATCC VR-2017).

No additional viral claims are required to support the potency testing, however applicants may submit additional effectiveness evidence against any specific virus claims indicated on their product's labelling.

2.2.4.2 Batch Replication Requirements and Number of Carriers or Replicates

- Testing against 1 sample of the product, representing 1 separately compounded batch, is required. The batch must be 1 of the 3 batches used for the sporicide test.
- Testing of 1 inoculated carrier per batch per virus is required.

2.2.4.3 Required Microbial Counts and Performance Standards

- A minimum recoverable endpoint viral titer after drying of 4 $\log_{10}$ per carrier is required;
- Complete inactivation of the virus must be demonstrated at all dilutions at the proposed contact time to support the effectiveness claim; and

- If cytotoxicity is present, a minimum 3 $\log_{10}$ reduction in viral titer beyond the cytotoxic level is required.

2.2.5 Fungicide Potency Testing

This section addresses potency testing requirements for the fungicide confirmatory requirement when the test method recommended in Appendix 5 is used.

2.2.5.1 Test Organisms

Effectiveness data is required against:

- *Trichophyton mentagrophytes* (ATCC 9533)

No additional fungal claims are required to support the potency testing, however applicants may submit additional effectiveness evidence against any specific fungal claims indicated on their product's labelling.

2.2.5.2 Batch Replication Requirements and Number of Carriers or Replicates

- Testing against 1 sample of the product, representing 1 separately compounded batch, is required. The batch must be 1 of the 3 batches used for the sporicide test.

2.2.5.3 Required Microbial Counts and Performance Standards

- A geometric mean of $1 \times 10^4 - 1 \times 10^5$ conidia per carrier (4 -5 $\log_{10}$ average density) is required for a valid test, unless otherwise prescribed in the test method.
- The test should be conducted at 5, 10 and 15 minute exposure times. All fungal spores should be killed at 10 and 15 minutes to support a 10 minute contact time.

2.2.6 Bactericide Potency Testing

This section addresses potency testing requirements for the bactericide confirmatory requirement when the test methods recommended in Appendix 6 are used.

2.2.6.1 Test Organisms

Effectiveness data is required against all of:

- *Salmonella enterica* (ATCC 10708)
- *Staphylococcus aureus* (ATCC 6538)
- *Pseudomonas aeruginosa* (ATCC 15442)

No additional vegetative bacterial claims are required to support the potency testing, however applicants may submit additional effectiveness evidence against any specific vegetative bacteria claims indicated on their product's labelling.

2.2.6.2 Batch Replication Requirements and Number of Carriers or Replicates

- Testing against 1 sample of the product, representing 1 separately compounded batch per bacterium is required. The batch must be 1 of the 3 batches used for the sporicide test.
- Testing of 60 inoculated carriers per batch per bacterium is required.

2.2.6.3 Required Microbial Counts and Performance Standards

The prescribed microbial counts and performance criteria as prescribed in the current test method must be met for a valid test.

2.3 Simulated-Use Testing and In-Use Testing

In addition to a product meeting the prescribed potency testing requirements, Health Canada recommends that simulated-use and in-use testing be conducted to verify the product's effectiveness when used to reprocess medical devices in accordance with the label's recommended conditions of use. The objective of these tests is to identify conditions under which the product may fail to meet its expected level of effectiveness. Therefore, negative results obtained from these tests should be used to establish more refined conditions for the use of the product, and applicants should ensure that the labelling for their products reflect the information gained from simulated-use and in-use testing (e.g., through the indication of limitations of use, adjustments to the directions for use, and appropriate precautionary statement labelling).

The following considerations should be met for all simulated-use and in-use testing:

- The test organisms used should be the most resistant organism for the claimed level of disinfectant activity (i.e., a suitable test microorganism for a sterilant would be *Bacillus subtilis* or *Clostridium sporogenes*; a suitable test microorganism for a high-level disinfectant would be *Mycobacterium bovis* BCG or alternatively *Mycobacterium terrae)*;
- The inoculum counts and performance criteria for a valid test should be the same as specified for the potency testing requirements (i.e., there should be no growth detected when a device is challenged with an inoculum of 6 $\log_{10}$);
- The same batches used for the sporicide potency testing should be used for the simulated-use and in-use testing; these should have been aged or stressed to "worst case" conditions.
- The microbial recovery methods should include brushing or rinsing the devices to ensure that all test microorganisms that are not killed will be detected, and the recovery solution should be inoculated into enrichment media.

The following sections provide specific device testing recommendations that applicants should take into consideration when developing simulated-use and in-use testing protocols to support the use of products as high-level disinfectants and sterilants on reusable semi-critical and critical medical devices. Health Canada encourages applicants to consult the ASTM E1837 and E2314 standards for examples of simulated-use test methods which have been developed to evaluate the effectiveness of cleaning and disinfection processes for reusable medical devices.

2.3.1 Simulated-Use Testing

Simulated-use testing is conducted in a controlled laboratory environment, and involves the precise application of specified and quantified inoculums to the surfaces of representative target devices (e.g., endoscopes, dental instruments). These tests evaluate the entire disinfection or sterilization process, including an appropriate pre-cleaning step, the treatment of the device with a proposed high-level disinfectant or sterilant, and then testing for microorganism recovery.

The following considerations are applicable for simulated-use testing:

- A number of different devices should be tested, consisting of different materials and design features; the sample size for testing should reflect the number and type of devices and materials specified on the product label.
- Applicants should ensure that the tests are performed on devices that are difficult to clean (e.g., those with small lumens, matt surfaces and hinges), that the most difficult areas for the disinfectant to penetrate and contact should be inoculated, and that the organic and inorganic challenge (i.e., soil load) that would be expected to be encountered and which is appropriate for the intended use of the device (e.g., blood or feces for endoscopes; blood or sputum for bronchoscopes) should be included.

2.3.2 In-Use Testing

In-use testing is conducted in a clinical setting by experienced personnel who have been trained on how to clean and treat medical devices according to the device labelling or to the protocols recommended by the clinical location (e.g., hospital medical device reprocessing protocols). The in-use testing should use multiple types of devices and should follow the labelled directions for use of proposed high-level disinfectants and sterilants, including any appropriate cleaning and terminal rinse steps.

2.4 Safety Requirements

The information in the following sections provides applicants with the safety data requirements considered necessary to support the safety of products intended for use as high-level disinfectants and sterilants on reusable semi-critical or critical medical devices.

2.4.1 Submission of Safety Data

Applicants are responsible for ensuring that their labelling specifies information that is representative of the potential safety hazards associated with a product when used and stored in accordance with the label's recommended conditions of use.

For high-level disinfectant and sterilant formulations which contain active or inert ingredients which have been previously characterised physically and toxicologically for their represented uses in reprocessing semi-critical and critical medical devices, the submission of existing compatibility testing and toxicity data as adequate evidence to establish its safety may be considered acceptable. Additionally, the submission of a scientific rationale based on the extrapolation of published hazard potentials(s) (e.g., from scientific literature references) for similar formulations or for the compatibility issues associated with device materials or classes of devices may be considered acceptable.

All safety data testing submitted should be conducted in accordance with Good Laboratory Practice (GLP) principles endorsed by Health Canada to ensure that the data is of high quality and reliable. Acceptable standards include those published by the Organisation for Economic Co-Operation and Development (OECD), and the United States Environmental Protection Agency (U.S. EPA), and the United States Food and Drug Administration (U.S. FDA). Applicants should refer to the guidance document referenced in Section 2.1.3 for information on providing evidence to Health Canada that safety studies adhere to the principles of Good Laboratory Practice.

2.4.2 Acute Toxicity Hazards

In developing appropriate labelling, the potential acute toxicity hazards associated with the use the product should be considered. It is recommended that applicants consider referencing the *Consumer Chemicals and Containers Regulations* and the *Controlled Products Regulations* for guidance on how to evaluate the hazards of a product. In general, the safety evaluation should be based on the product as sold in its marketed container (e.g., the concentrated form of the product, for products that are intended to be diluted before use), however, depending on the intended use of the product and the ingredients within the product formulation, the hazard profile of the use-dilution may also be considered in order to appropriately address the acute toxicity hazards associated with the use of the product.

In lieu of conducting acute toxicity testing for a proposed product, Health Canada may consider existing acute toxicity hazard reviews or information from other published scientific sources for similar formulations to be adequate evidence to support the safety of a proposed product, provided that these sources address the potential toxicity hazards of both the active and inert ingredients within the product's formulation. Additionally,

applicants may choose to reference acute toxicity hazard information prepared for other purposes (e.g., specified in a Material Safety Data Sheet) for a proposed product. As a result, the submission of a rationale to support the safety of a proposed product based on the extrapolation of acute toxicity hazard information from these sources is generally considered acceptable. However, for products that do require the submission and evaluation of safety data as part of their application process, applicants are encouraged to contact Health Canada in advance of submitting an application to determine the specific safety data requirements that may be considered necessary.

Common short-term exposure endpoints which should be evaluated for all proposed products include the following, with recommended test protocols published by the Organisation for Economic Co-Operation and Development referenced:

- Acute Oral Toxicity (LD_{50}) (OECD 420, 423 or 425)
- Acute Dermal Toxicity (LD_{50}) (OECD 402)
- Acute Inhalation Toxicity (LC_{50}) (OECD 403)
- Acute Dermal Irritation (OECD 404)
- Acute Eye Irritation (OECD 405)
- Dermal Sensitization (OECD 406 or 429)

2.4.3 Physical and Chemical Hazards

In developing appropriate labelling, the potential physical and chemical hazards associated with their use and storage should be considered (e.g., flammability, explodability, potential for chemical incompatibility). It is recommended that applicants consider referencing the *Consumer Chemicals and Containers Regulations* and the *Controlled Products Regulations* for guidance on how to evaluate the hazards of a product. In general, the safety evaluation of a proposed product should be based on the product as sold in its marketed container (e.g., the concentrated form of the product, for products that are intended to be diluted before use), however, depending on the intended use of the product and the ingredients within the product formulation, the hazard profile of the use-dilution may also be considered in order to appropriately address the physical and chemical toxicity hazards associated with the use of the product.

In lieu of conducting physical or chemical hazard testing for a proposed product, Health Canada may consider existing hazard reviews or information from other published scientific sources for similar formulations to be adequate evidence to support the safety of a proposed product. Additionally, applicants may choose to reference physical or chemical hazard information prepared for other purposes (e.g., specified in a Material Safety Data Sheet) for a proposed product. As a result, the submission of a rationale to support the safety of a proposed product based on the extrapolation of physical and chemical hazard information from these sources is generally considered acceptable.

However, for proposed products that require the submission and evaluation of safety data as part of their application process, applicants are encouraged to contact Health Canada in advance of submitting an application in to determine the specific safety data requirements that may be considered necessary.

2.4.4 Device Compatibility Testing

Chemical products used to reprocess medical devices have the potential to damage the devices or lead to deterioration of the materials, and thus adversely affect the safety and effectiveness of the reprocessed device. Therefore, the submission of data confirming the compatibility of high-level disinfectants and sterilants with the recommended medical devices and component materials that are indicated within the product's labelling is considered necessary. Applicants should consider common classes of device materials (e.g., metals, polymers) and common classes of devices (e.g., endoscopes) which a potential user could be expected to reprocess.

For products with formulations which have shown a history of use and compatibility with materials commonly used in the construction of reusable medical devices, the absence of problem reports may be regarded as substantive evidence for the compatibility between the product and medical devices fabricated with these component materials. Similarly, if the labelling for a specific device indicates compatibility with general classes of high-level disinfectants and sterilants (e.g., immersion in a gluteraldehyde-based formulation; reprocessing in a hydrogen peroxide gas plasma chemiclave sterilizer), then there may be no need to conduct additional testing on that device and rather the labelling could claim compatibility against that specific device.

When device or material compatibility has to be demonstrated, compatibility should be demonstrated by exposure under simulated-use conditions. Prior to the exposure of a target device to a proposed high-level disinfectant or sterilant, the device and material should be characterized using suitable physical and chemical analysis. Following exposure to the disinfectant the device should be inspected for signs of deterioration or change which may have an effect on the device's intended use and performance (e.g., pitting, colour changes, dimensional changes). If the results following exposure are the same as those for the baseline characterization, compatibility is supported.

For the validation of a compatibility claim, it is expected that target devices should be repeatedly exposed to a proposed disinfectant at the maximum specified use concentration and for the maximum contact time indicated in the product's labelling. Applicants should provide a justification for the selection of the number of reprocessing cycles used for the compatibility testing. Given that quantifiable deterioration may not be significantly exhibited until a large number of reprocessing cycles have occurred, and in

order to minimize the extent of testing, applicants may provide a rationale for the projected compatibility for a device or material based upon extrapolations.

Additional compatibility considerations that applicants should address, where appropriate, include:

- Compatibility with common container materials (e.g., metals, polymers) used to hold the product (e.g., disinfectants recommended for use in immersion baths); and
- Compatibility with cleaning agents (e.g., detergents, enzyme cleaners) used to pre-clean medical devices.

2.4.5 Process Residue Toxicity Testing

Following the use of a disinfectant to reprocess medical devices, residues from the product may remain on the device. Therefore, it is recommended that the repeated-dose toxicity hazards for a proposed disinfectant be evaluated to address the potential toxicity consequences (i.e., biocompatibility) of product residues remaining on reprocessed semi-critical and critical medical devices, and to determine whether a terminal rinse step should be indicated in the labelling.

When toxicity testing has to be conducted for a proposed product, due to adequate justification not being available in published reports or through scientific literature references, the hazard potential of the product residues should be evaluated based on testing following exposure to the product under simulated-use conditions at the maximum specified concentration and for the maximum contact time indicated in the product's labelling. The following exposure endpoints should be considered, with recommended test methods published by the Organisation for Economic Co-Operation and Development (OECD) or International Organization for Standardization (ISO) referenced:

- Cytotoxicity (ISO 10993-5)
- Repeated-Dose Toxicity (OECD 407, 408, 409, 411 or 422)
- Teratogenicity (OECD 414)
- Genotoxicity (OECD 471, 473, 474, 475)
- Chronic/Carcinogenicity (OECD 451, 453)

Applicants should take note of the following considerations:

- For the repeated-dose toxicity endpoint, at a minimum an oral exposure test should be conducted with a duration of a minimum of 29 days and a maximum of 90 days, and the method should include a comprehensive histological, clinical biochemistry and haematological evaluation.

- The testing of genotoxicity is recommended as a screening program to identify substances which might cause permanent transmissible changes.
- A chronic/carcinogenicity study is recommended when genotoxicity studies yield clear or equivocal findings. For a proposed product containing such a compound, an unequivocal absence of carcinogenicity at doses approaching the Maximum Tolerated Dose should be demonstrated.

The amount of residue that remains on a target device may vary depending upon the conditions of use of the product, the specific component materials of the device, and the methods used to reduce residuals prior to reuse (e.g., a terminal rinse step with sterile water). Applicants should submit a description of the residue extraction method that was used for the toxicity testing and provide information on how the type and amount of the residue was determined. If the data from the toxicity tests shows that an acceptable (i.e., non-toxic) level of residue is present in the extracted residue tested, then any residues remaining on the device are expected to be present at an acceptable level. It is recommended that multiple dose levels of the residue be used to construct a dose-response curve to which the actual residue level can be compared during a risk assessment process.

3. EFFECTIVE DATE

This guidance document will come into effect immediately upon the date of publication. All disinfectant medical device licence applications received after the effective date are expected to be filed with the updated supporting data requirements.

APPENDICES

Appendix 1: References

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Appendix 2: Sporical Potency Testing - Sterilant and High Level Disinfectants

Table 1: Sporical Potency Testing – Sterilant and High Level Disinfectants

Claim	Recommended Test Methods	Test Organisms	Number of Batches per Organism & Replicates or Carriers per Batch	Inoculum Count or Carrier Count	Performance Criteria for Effectiveness
Sterilant	• AOAC 966.04 *For vapour or gas products*: Expose carriers to test product in the intended specific device according to the directions for use of the device.	*Bacillus subtilis* (ATCC 19659) (*use Method II of AOAC 966.04*) AND *Clostridium sporogenes* (ATCC 3584) (*use Method I of AOAC 966.04*)	•3 batches •2 types of carriers (suture loop and porcelain penicylinder, as prescribed in current version of test method) •60 carriers per type per batch	Unless otherwise prescribed: • Titer of spore suspension high enough to achieve mean of 1 x 10^5 - 1 x 10^6 spores per carrier.	• 60/60 carriers negative for growth per batch per carrier at proposed contact time.
High-Level Disinfectant					• 59/60 carriers negative for growth per batch per carrier in less than 10 hours.

Appendix 3: Mycobactericide Potency Testing

Table 2: Mycobactericide Potency Testing

Claim	Recommended Test Methods	Test Organisms	Number of Batches per Organism & Replicates or Carriers per Batch	Inoculum Count or Carrier Count	Performance Criteria for Effectiveness
Mycobactericide / Tuberculocide	• AOAC 965.12 • US EPA QTB[1]	An appropriate *Mycobacterium* species, such as: *Mycobacterium bovis* (BCG)	• 2 batches *(must be 2 of the 3 batches used for sporicidal test)* • 10 carriers *For QTB:* • 4 replicates per batch	As prescribed in current test methods. *For AOAC 965.12*: Unless otherwise prescribed: • A minimum geometric mean of 1 x 10^6 CFU per carrier is required. • The inoculum may need to be appropriately concentrated or adjusted to achieve this minimum requirement.	As prescribed in current test methods & at proposed contact time. *For AOAC 965.12:* Unless otherwise prescribed: • 10/10 carriers negative for growth per batch at the specified contact time; and • No growth in any of the inoculated subculture media. *For QTB:* • A minimum 99.9999% reduction is required.

1. The US EPA Quantitative Tuberculocidal Test Method (QTB) is only recommended for gluteraldehyde-based products, which have not been validated in the AOAC 965.12 method. This method is based on the research of Ascenzi *et al.*

Appendix 4: Virucide Potency Testing

Table 3: Virucide Potency Testing

Claim	Recommended Test Methods	Test Organisms	Number of Batches per Organism & Replicates or Carriers per Batch	Inoculum Count or Carrier Count	Performance Criteria for Effectiveness
Virucide	• ASTM E1053	Any virus may be tested, however Health Canada encourages testing using one the following viruses: • Poliovirus type 1, Chat strain ATCC VR-162 • Human Adenovirus type 5 – ATCC VR-5 – ATCC VR-1516 • Bovine Parvovirus ATCC VR-767 • Canine Parvovirus ATCC VR-2017	• 1 batch *(must be 1 of the 3 batches used for sporicidal test)* • 1carrier *For effectiveness testing against the human Hepatitis B virus, Hepatitis C virus and Norovirus using surrogate viruses, 2 carriers are required testing.*[1]	As prescribed in current test methods. Unless otherwise prescribed: • A minimum recoverable endpoint viral titer after drying of 4 $\log_{10}$ per carrier is required.	As prescribed in current test methods & at proposed contact time. Unless otherwise prescribed: • Complete inactivation of the virus at all dilutions at proposed contact time; and • If cytotoxicity is present, a minimum 3 $\log_{10}$ reduction in viral titer beyond the cytotoxic level for all the test carriers is required.

1. Effectivenss testing should be conducted using the protocols developed by the U.S. EPA using surrogate viruses (i.e., using duck hepatitis B virus for the human hepatitis B virus; using bovine viral diarrhea virus for the human hepatitis c virus; and using feline calicivirus for human norovirus).

Appendix 5: Fungicide Potency Testing

Table 4: Fungicide Potency Testing

Claim	Recommended Test Methods	Test Organisms	Number of Batches per Organism & Replicates or Carriers per Batch	Inoculum Count or Carrier Count	Performance Criteria for Effectiveness
Fungicide	• AOAC 955.17	*Trichophyton mentagrophytes* (ATCC 9533)	• 1 batch *(must be 1 of the 3 batches used for sporicidal test)*	As prescribed in current test method. Unless otherwise prescribed: • The inoculum employed should be modified to provide a geometric mean of $1 \times 10^4 - 1 \times 10^5$ conidia per carrier (4 -5 $\log_{10}$ average density).	As prescribed in current test method & at proposed contact time. *For AOAC 955.17*: • The test should be conducted at 5, 10 and 15 minute exposure times. • All fungal spores should be killed at 10 and 15 minutes to support a 10 minute contact time.

Appendix 6: Bactericide Potency Testing

Table 5: Bactericide Potency Testing

Claim	Recommended Test Methods	Test Organisms	Number of Batches per Organism & Replicates or Carriers per Batch	Inoculum Count or Carrier Count	Performance Criteria for Effectiveness
Bactericide	AOAC Use-Dilution Method • 955.14 • 955.15 • 964.02	*Salmonella enterica* (ATCC 10708) AND *Staphylococcus aureus* (ATCC 6538) AND *Pseudomonas aeruginosa* (ATCC 15442)	• 1 batch *(must be 1 of the 3 batches used for sporicidal test)* • 60 carriers	As prescribed in current test methods.	As prescribed in current test methods & at proposed contact time.

Appendix 7: Labelling Considerations for High-Level Disinfectants and Sterilants

This section is intended to assist applicants in preparing appropriate labelling for high-level disinfectants and sterilants; however, these are labelling **recommendations only** and are **not** regulatory requirements. These labelling considerations are intended to address the regulatory requirement for adequate directions for all intended uses of a disinfectant devices to be indicated on its labelling.

1.0 Type of Medical Device

The category of medical devices for which the product is recommended for use should be specified on the label (i.e., semi-critical or critical) with relevant examples of the types of devices (e.g., laparoscopes, endoscopes, stethoscopes). The label should refer a user to consult the labelling for a target device prior to reprocessing with a high-level disinfectant or sterilant, in order to ensure that the manufacturer recommendations for device decontamination are followed (e.g., to identify potential material incompatibilities).

Health Canada considers that in lieu of testing being performed on certain device features (e.g. small lumens), or in the case that the simulated use or in-use testing fails to meet the appropriate performance criterion for devices with these certain features, that the labelling should exclude the use of the proposed high-level disinfectant or sterilant on devices with these features.

2.0 Pre-Cleaning

The labelling should indicate a pre-cleaning step prior to the use of the product as a high-level disinfectant or sterilant. The label should refer the user to consult the labelling for a target device prior to pre-cleaning devices, in order to ensure that the manufacturer's recommendations for device decontamination are followed. A statement to the effect of the following may be appropriate:

- Clean devices thoroughly prior to disinfection or sterilization to remove all blood and patient material that may inactivate the active agent.

3.0 Addition of Activator

Products that are intended to have an activator added prior to their use should specify the volume and directions for the addition of the activator.

Additionally, the amount of time that an activated solution may be stored or used without a decrease in efficacy should be specified. Products that are intended to be activated and stored for an extended period of time (i.e., the label indicates that the activated solution remains effective

for a defined number of days after preparation) should have efficacy data or a scientific rationale approved to support the claim. Otherwise, the labelling should clearly specify that the product is to be activated immediately before being used.

4.0 Temperature

When an ambient temperature is not specified in the directions for use of products represented for use on environmental surfaces, a temperature of 18-25^{o}C may be assumed. Products that have been tested and found to be effective at temperatures other than 18-25^{o}C (e.g., disinfectants for use in heated immersion baths) should specify in their directions for use that heating or cooling to the specified temperature is required prior to disinfection.

5.0 Material and Device Compatibility Issues

The potential for material and device compatibility issues between target devices and a proposed product should be specified on the label. The label should refer the user to consult the labelling for a target device, in order to ensure that the manufacturer's recommendations for device decontamination are followed. A statement to the effect of the following may be appropriate for products with established incompatibility concerns:

- Do not use with the following devices/materials: [List devices/materials that have been shown to be incompatible with the product.] Testing has shown that the product is not compatible with these devices/materials.

6.0 Sterilants for Use in a Chemiclave Sterilizer

The labelling for a sterilant which is a gas/vapour/plasma (e.g., hydrogen peroxide gas plasma, ethylene oxide) and is recommended for use in a specific device (i.e., a chemiclave sterilizer) should specify the type of chemiclave (make, model, etc.) and the cycle (temperature, time, pressure, etc.) with which the disinfectant is intended to be used.

7.0 Products with Re-Use Applications

Products which are intended for re-use applications (e.g., disinfectants intended for use in immersion baths) should provide adequate labelling directions for the user on the duration of time that the product may be re-used without a decrease in the effectiveness of the product.

8.0 Chemical Test Strips and Biological Indicators

If applicable, the use of any chemical test strips or biological indicators recommended for a product should be specified on the label (e.g., to determine the pH or active ingredient concentration).

9.0 Terminal Rinse Step

The labelling should indicate any recommended terminal rinse steps following the use of the product to remove potential residues remaining on reprocessed devices. Applicants should ensure that rinse procedures for semi-critical and critical medical devices do not compromise the achieved level of disinfection (i.e., high level disinfection or sterility, respectively). A statement to the effect of the following may be appropriate:

- Rinse devices thoroughly following disinfection or sterilization with [List an appropriate rinse, such as sterile water] to remove toxic residues.

Applicants should ensure that when the labelling of a high-level disinfectant or sterilant indicates a terminal rinse step that detailed rinsing instructions are provided, including the type, temperature and volume of rinse water necessary to remove residues as determined from the toxicity testing. Saline solutions are not recommended for the final rinse because saline solutions may lead to corrosion after drying on certain devices as well as to the build-up of inorganic residues.

10.0 Hazard Classification Criteria and Precautionary Statements

It is recommended that applicants consider referencing the *Consumer Chemicals and Containers Regulations* for guidance on hazard classification criteria and the associated precautionary and hazard statements which may be appropriate for high-level disinfectants and sterilants.

Appropriate precautionary statements should be clearly and prominently specified on the labelling of high-level disinfectants and sterilants to ensure the safety of the product when it is used in accordance with the label directions. The precautionary statements must be relevant to the potential acute toxicity exposure hazards of the product.

10.1 Warning Statements

Labels should indicate the following statements:

- Read the label before using; and
- Keep out of reach of children.

10.2 Signal Words and Primary Hazard Statements

Appropriate signal words (e.g., Danger, Poison, Warning, and Caution) and primary hazard statements (e.g., Corrosive, Irritant) should be indicated on labels, as appropriate for the potential acute toxicity hazards of the product.

10.3 Hazards to Humans and Domestic Animals

Specific hazard statements should be indicated on labels, as appropriate for the potential acute toxicity hazards to humans and domestic animals of the product (e.g., Fatal if swallowed; Corrosive – Causes severe eye damage; Causes skin irritation – Do not get on skin or on clothing).

10.4 Personal Protective Equipment

Personal protective equipment statements should be indicated on labels, as appropriate for the potential acute toxicity hazards of the product, in order to ensure the safety of the product when it is used in accordance with the label directions. The type of personal protective equipment specified should be appropriate to the potential hazard to a user, and include: protective clothing, protective footwear, chemical-resistant gloves, protective eyewear, and respiratory protective devices.

10.5 First Aid Statements

First aid statements should be indicated on labels, as appropriate for the potential acute toxicity hazards of the product (e.g., for accidental ingestion, inhalation, eye contact, skin contact, and for accidental injuries requiring medical attention).

10.6 Physical and Chemical Hazard Statements

Physical and chemical hazard statements should be indicated on labels, as appropriate to the potential physical and chemical hazards of the product (e.g., flammability, explodability, and chemical incompatibility). For products with known chemical incompatibilities, a hazard statement may be appropriate on the label (e.g., sodium hypochlorite forms toxic chlorine gas when mixed with acids or ammonia compounds).

11.0 Storage Instructions

Storage instructions appropriate for the level of hazard and packaging should be indicated on the label, and should address the factors which might alter the shelf-life of the product (e.g., temperature extremes, excessive moisture, heat or humidity, sunlight). One or more statements to the effect of the following may be appropriate:

- Storage at room temperature / Store at 15-30^{o}C.
- Store in a cool, dry place.
- Store tightly closed in a cool, dry place in original container away from sunlight.
- Do not freeze.

12.0 Disposal Instructions

Disposal instructions appropriate for the level of hazard and packaging should be indicated on the label, and should provide sufficient information on how to appropriately dispose of the product container and any unused product. Applicants should contact municipal/provincial/territorial product stewardship organization(s) for information on how to manage the life cycle of their chemical products. One or more statements to the effect of the following may be appropriate:

- For information on disposal of unused, unwanted product, contact the manufacturer or the appropriate municipal/provincial/territorial agency or product stewardship organization.
- Rinse the emptied container thoroughly prior to disposal.
- Non-refillable container / Do not reuse or refill this container.
- Dispose of the empty container in accordance with municipal/provincial/territorial requirements. Offer for recycling, if available.