



Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

DRAFT

**GUIDELINES
FOR THE EVALUATION
OF HOUSEHOLD/COMMERCIAL AND HOSPITAL
GRADE DISINFECTANTS**

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GUIDELINES FOR THE EVALUATION OF STERILANTS AND DISINFECTANTS

1. INTRODUCTION

These guidelines describe the information to be supplied to the Therapeutic Goods Administration (TGA) for the inclusion of disinfectants on the Australian Register of Therapeutic Goods (ARTG). They also serve as a guide to those sponsors of disinfectants who are exempted from listing their products but whose products have to meet the requirements of Therapeutic Goods Order No 54.

Enquiries concerning the applications for inclusion should be directed to the Section Head, Application Entry and Coordination Section, Office of Devices, Blood and Tissues (ODBT), on phone (02) 6232 8613. Applicants should note that all relevant aspects of these guidelines must be addressed in their application and accompanying data submission.

Substantial deficiencies in the completeness or rigour of material provided for evaluation will result in the application being rejected. New fees will be payable if a rejected application is resubmitted. Sponsors must provide a table of contents indexed to all pages in the accompanying data submission. The submission should be filed in a hard cover loose-leaf binder complete with cover page, tabs for major sections, and unique volume and copy identified. Where data is contained in more than one volume then the indexing system used should indicate the particular volume number and then the total number of volumes submitted eg. Volume 2 of 3. Where multiple copies of the same data are submitted then copy 1, copy 2 can be used for indexing. All data must be in English.

Data submitted to the TGA will be treated as 'commercial-in-confidence' at all times. It should be noted that submitted data will be retained and will not usually be returned to the applicant after the evaluation is completed.

The following descriptions are provided for the convenience of the reader. Definitions for these and other types of disinfectants are given in the 'Standard for Disinfectants and Sterilants', Therapeutic goods Orders Nos. 54 and 54A.

Hospital grade disinfectants are suitable for general disinfection of hard surfaces, for example building and fitting surfaces, and for purposes not involving instruments or surfaces likely to come into contact with broken skin. These preparations are designed for general use on inanimate surfaces (other than instruments) in medical, dental, beauty therapy and hairdressing facilities, premises involved in the manufacture of therapeutic goods (ie cleanrooms) as well as in the home.

Household/commercial grade disinfectants are suitable for general purpose disinfecting of building or fitting surfaces, and for other purposes, in premises or involving procedures other than those specified for a hospital grade disinfectant.

For hospital or household/commercial grade disinfectants with specified biocidal claims, the data requirements are less stringent since these products are used for general disinfection of contaminated surfaces eg. benches, floors and are unlikely to come in contact with the patient if used in accordance with the sponsor's labelled instructions.

A **specific claim** is a claim which covers virucidal, sporicidal, tuberculocidal, fungicidal or other biocidal activity. Except where claims of activity against fungi (yeasts and moulds) for *excluded products* are concerned, such claims lift a product into the category of goods requiring a safety evaluation.

A **non-specific claim** is a claim which includes general antibacterial action or activity against

bacteria covered by the battery of test organisms included in the specified test, or bacteria of the same family. Claims for bacteria other than these are allowable and do not cause the product to become registrable, but the particular organism against which activity is claimed must be included as an extra organism in the test battery eg. *E. coli O157*, *Salmonella spp*, *Streptococcus spp*, etc.

For administrative purposes, disinfectants can be listed on the ARTG (with or without a safety evaluation), exempted from registration and listing or excluded from TGA regulation. There is also provision for grouping some types of disinfectants on the Australian Register of Therapeutic Goods - see grouping of products at Appendix E

A safety evaluation entails an assessment by the TGA of the results of testing conducted in accordance with the requirements of this TGO in order to demonstrate compliance with the performance requirements in relation to the claims made.

Listed Disinfectants requiring a safety evaluation include any disinfectant for which a specific claim is made (see above) and disinfectants of any category (including otherwise Exempt goods) where the active or an excipient is a new chemical entity. (A new chemical entity is either a disinfectant active which is not included as an active in an existing product on the ARTG, or a disinfectant excipient which is not included on either the Australian Inventory of Chemical Substances (AICS) or the ARTG).

Listed Disinfectants not requiring a safety evaluation are hospital grade disinfectants with and without specific biocidal claims and household/commercial grade disinfectants with specific biocidal claims except where the active or an excipient is a new chemical entity.

Test certificates and any other evidence needed to support an application for listing and to demonstrate compliance with TGO 54 should be held by the manufacturer or sponsor. This information may be called for examination by the TGA if a problem arises with the product. While manufacturers/sponsors are not required to submit detailed data as part of the listing process, there is a requirement that the product meets TGO 54.

Exempt goods are household/commercial grade disinfectants without specific biocidal claims. They are not required to be listed on the ARTG, and therefore no application is required. However these goods must comply with certain parts of TGO 54. Household/commercial grade disinfectants are all required to meet the labelling requirements as set out in Clause 4 of TGO 54, as well as comply with performance requirements set out in Clause 3 (6) of TGO 54. Sponsors must supply evidence of compliance with TGO 54 when requested by the TGA.

Exemption from entry on the ARTG does not apply where the product contains a new chemical entity as the active ingredient, or an excipient not already listed on the AICS or ARTG. In this case, the product becomes listable with a safety evaluation.

Excluded goods are products such as sanitisers, cleaners, deodorisers and cleaning wipes (where claims are limited to activity within the wipe only), which are covered by a Section 7 Order made under the Therapeutic Goods Act. Products covered by a Section 7 Order are formally excluded from all requirements of the Therapeutic Goods Act including TGO 54. These goods cannot make claims that they are disinfectants, either directly or by implication. Permissible claims for excluded goods are specified in Appendix F.

2. INFORMATION TO BE PROVIDED

2.1 This section should act as a checklist for applicants.

Some or all of the following information must be provided to the TGA as part of the application for listing of sterilants and disinfectants. Table 1 sets out those elements of information listed in 2.1.(b) which needs to be addressed by applicants when submitting applications to list sterilants and disinfectants which require a safety evaluation. If in doubt about data requirements then it would be prudent for applicants to resolve these concerns with ODBT before preparing their detailed submissions.

- a) A completed *Therapeutic Devices Application*.
- b) Specific information (see also Table 1 and TGO 54/54A)
 - i. The common name of the product and the trade name if applicable.
 - ii. The name and address of the Australian sponsor and all persons/companies involved in each step of the manufacture of the product.
 - iii. History and development of the product.
 - iv. Material Safety Data Sheet and risks associated with the product's use.
 - v. The formula of the product.
 - vi. A brief description of the method of manufacture of the product.
 - vii. Quality specifications applicable to the product and details of the methods of analyses used, including details of method validation.
 - viii. Details of all pack sizes, description of packs.
 - ix. A copy of the labelling.
 - x. Storage requirements and shelf life.
 - xi. Stability data in support of the shelf life at or above the maximum recommended storage temperature. Include details of when the studies were carried out and the methods of analysis used.
 - xii. Instructions for use.
 - xiii. Specific biocidal claims made for the product including the time taken to achieve the biocidal effect and the temperature.
 - xiv. Microbial efficacy data in support of the biocidal claims. xv. Toxicity information on disinfectant residue eluates and/or disinfectant, as appropriate (refer Appendix C)

For products of any grade where the active or an excipient is a new chemical entity, full set of toxicology data is required. The data required is similar to

that required by the National Occupational Health and Safety Commission for a full notification under the National Industrial Chemicals Notification and Assessment Scheme (NICNAS).

TABLE 1 Information required by TGA for ARTG inclusion for each category of disinfectant.

	CATEGORY OF DISINFECTANT	ARTG STATUS	INFORMATION REQUIRED†
A	HOSPITAL GRADE DISINFECTANTS (with specific claims)	Listable	All of 2.1. (b), except xvii.
B	HOSPITAL GRADE DISINFECTANTS (no specific claims)	Listable	All of 2.1. (b), except iii, iv v, vii, viii, xiv-xvii.
C	HOUSEHOLD/COMMERCIAL GRADE DISINFECTANTS (with specific claims)	Listable	All of 2.1. (b) except iii, xvi and xvii.
D	HOUSEHOLD/COMMERCIAL GRADE DISINFECTANTS (no specific claims)	Exempt*	No application is required. These products are required to comply with the labelling and performance requirements of TGO 54/54A. Evidence must be available for review if requested by the TGA.
E	SANITISERS, CLEANERS, DEODORISERS AND CLEANING WIPES & Antibacterial clothes preparations (complying with a Section 7 Order under the <i>Therapeutic Goods Act</i>)	Excluded	Must be covered by a section 7 Order under the <i>Therapeutic Goods Act</i> to be excluded from TGA regulatory controls.

* products in this category become Listable if they contain an active or an excipient that is a new chemical entity.

† refers to the Guidelines for the Submission of Applications and Data for the Registration and Listing of Sterilants and Disinfectants, paragraph 2.1.

For an explanation of the terms used in this table see pages 4, 5 and 6.

3. EXPLANATORY NOTES

3.1 *Common name of the product and the trade name if applicable*

The common name of the product includes details of the trade name and other name by which the product is known and is the name to be used on the label (see acceptable common names in Schedule 2 of TGO 54).

3.2 *The name and the address of the Australian sponsor, and all persons/companies involved in each step of the manufacture of the product*

The legislation requires full details of the Australian sponsor and all companies involved in each step in the manufacture of the product eg. those who manufacture the active ingredients, those who manufacture or contract manufacture the formulated product, companies filling, packing and labelling the product, companies involved in the quality control testing and stability testing the product. The manufacturing site address is required for those companies involved in the manufacture of the product.

3.3 *History and development of the product*

Describe briefly the history, origins and development of the product, and particularly whether it is a modification of an existing product or a new product. Information to help determine any risks associated with the product and the level of evaluation/information is needed here. If this type of product has not been previously supplied in Australia then provide the date of marketing/approval in overseas countries.

A summary is required of local and overseas adverse incidents reported relating to safety or efficacy of the product since the introduction of the product in the market. Details are required of any regulatory action relating to the product in any country, either completed, current or forthcoming, including certificates or notifications where appropriate, eg. rejection of marketing approval, recall, hazard alert.

3.4 *Risk analysis*

The intention of this part is to assure the TGA that the product developer has considered aspects that are unique to the product and the environment in which it is intended to be used. The information provided does not need to be extensive but should identify the major risks associated with the use of the product, how these have been addressed. For example, a reformulated product containing a new chemical entity may have increased risks in relation to stability and toxicity when compared with the previous formulation of the product supplied over several years.

3.5 *The formula of the product*

Full details are required of the formulation for each strength of the product(s) supplied. Percentages are not acceptable unless expressed as a percentage of the total mass or volume of the disinfectant with the units specified. The nominal amounts expressed as the mass or volume of each ingredient added to the nominal formulation are required.

The chemical name (Australian Approved Name) of all active and inactive ingredients must be provided if available. When an AAN is not available then sufficient information should be provided to assist the TGA to determine the AAN. Sources of information include: the chemical name, proprietary ingredient name (and manufacturer's name), manufacturers' chemical data sheets, Merck Index, published scientific literature on the compound/mixture. Sponsors should note that there are a number of proprietary additives, excipients recorded on the ARTG. As this information is confidential to the provider it cannot be released to other interested parties. You should check with your supplier if their product is currently included on the ARTG and if so, quote the ARTG number. A publication of AAN's is available from the TGA Publications Office.

For new chemical entities for use as disinfectants, details of the method of synthesis/biosynthesis, patents applicable, and quality control may be required. Applicants should discuss any concerns with the TGA before submitting the application. For new chemical entities the approval process may include referral to the NDPSC for scheduling as appropriate. For established disinfectant actives, the TGA may at a later time request details of the manufacture of the actives.

3.6 *A brief description of the method of manufacture of the product*

A short summary of the key steps in the manufacture of the formulated product is required. Give information about acceptance testing of active starting materials, excipients and specifications/standards applicable to these ingredients, give processing details eg stir until dissolved, heat to 60°C, and any in-process testing (include specifications) to control the outcome of the process.

3.7 *Quality specifications applicable to the product and details of the methods of analyses used, including details of method validation*

A full account is required of the physical and chemical specifications applicable to the finished product at the time of batch release and those applicable throughout the shelf life of the product up until expiry is reached. It is considered good manufacturing practice for manufacturers to adopt more stringent specifications for the purpose of releasing batches, if the key active ingredients are relatively unstable and are likely to deteriorate over the shelf life period.

By setting more stringent limits at the time of batch release, then it is more likely that the all of shelf life (expiry) limits will be met for the nominated period and conditions of storage.

3.8 *Details of all pack sizes, description of packs and containers*

Containers used for disinfectants and sterilants need to be fit for the purpose. They should be impervious to transpiration of the contents through the container wall, and not react chemically with the contents. The container should not leach plasticisers and other wall components into the contents on standing for protracted periods of time. Containers should be sufficiently strong to prevent leakage arising from ordinary risks of handling, storage, or transport, and should have sufficient excess capacity to provide an ullage space to reduce risks of damage due to expansion of the contents when handled and stored. Manufacturers of sterilants and disinfectants should cover these points when evaluating suppliers of containers for their products, and have these records available if requested by the TGA in the event of a complaint.

Applicants are advised to consult sections 50-61 of SUSDP²⁸, which outline the requirements for containers holding poisons and the relevant Australian standards applicable to containers. The requirements of the Australian Dangerous Goods Code should be observed.

3.9 A copy of the labelling for all pack sizes (if different)

Labelling includes the label affixed to the immediate container, the primary pack (where relevant), any package insert which accompanies the disinfectant, and or any other information which is given about the indications for use of the disinfectant. Advertising must be restricted to indications included in the ARTG.

Labelling must comply with TGO 54 as well as the requirements of the SUSDP²⁸. Labelling should also comply with any requirements or recommendations in the documents, “List of Designated Hazardous Substances” or “Approved Criteria for Classifying Substances” as appropriate.

Submitted labelling may take the form of draft artwork. Applicants are advised to have their labelling and packaging approved by the TGA before placing orders with the printer. Where information such as batch numbering and expiry coding is added at the time the product is packed and labelled then an explanation about the location of the information should be given.

The label should state:

- a) approved name(s) of active ingredient(s);
- b) common name;
- c) quantity/proportions of active ingredients(s) in mg/mL or mg/G, and the proportion of available chlorine/bromine/iodine if applicable;
- d) quantity of disinfectant/sterilant;
- e) batch number;
- f) expiry date;
- g) there is no requirement for AUST L (Listed disinfectants) numbers to be placed on labels but sponsors are encouraged to include them;
- h) name and address of the Australian manufacturer or sponsor;
- i) clear and adequate instructions for use - see 3.13 *Instructions for use*.

3.10 Storage requirements and shelf life of the product

Information about the storage conditions applicable to the goods and the nominal shelf life for the product shall be included in the submission. Standard statements about the expiry date must be selected from those given in TGO 54.

3.11 *Stability data in support of the shelf life and the maximum recommended storage temperature*

This data should be determined in accordance with the information given at Appendix C, *Guidelines for stability testing of disinfectants and sterilants*, and submitted for evaluation by the TGA. Applicants are reminded to include details of when the studies were carried out and the methods of analysis used. Microbial efficacy stability data generated at the end of the shelf life may be forwarded later, if not available at the time of application.

3.12 *Instructions for use*

Detailed information should be provided in the submission on how to prepare the disinfectant and use it to ensure specifications are met, as well as installation instructions for disinfecting and sterilising systems (if applicable).

It is important to identify any limitations on the use of the disinfectant and cover the operational conditions which must be observed when reusing the disinfectant. Where relevant, the detailed descriptive information for the packs should also include information about any test strips and chemical indicators provided/required for monitoring the efficacy of the disinfectant.

Where it is stated that diluted disinfectant can be stored for protracted periods then chemical stability and microbial efficacy studies should validate the advice given. The exact period of storage should be specified as both chemical and microbial efficacy stability data will be required to demonstrate the disinfectant remains potent for the nominated period of time.

3.13 *Specific biocidal claims made for the product including the time taken to achieve the biocidal effect*

A statement detailing these claims is to be provided. All claims should be listed with exposure time and temperature of use clearly stated eg.

Kills vegetative bacteria in 10 minutes at 20 °C.

Tuberculocidal in 20 minutes at 20 °C.

Where possible, multiple temperatures of use should be avoided - a single temperature of use is preferred where a temperature of use is specified on the label the Microbial efficacy tests are to be carried out at the temperature specified on the label.

3.14 *Microbial efficacy data in support of the biocidal claims*

Data is required as set out in Appendix A *Guidelines for submitting data supporting the microbial efficacy of sterilants and disinfectants*, for the level/grade of disinfectant or sterilant at the minimum effective concentration (MEC) or the minimum recommended concentration (MRC) at the end of the shelf life. Tests may not necessarily be conducted on the product at the end of shelf life if data is to be provided for initial registration purposes, however, the tests detailed in Appendix C will need to be carried out at the end of the shelf life and when the shelf life is to be extended (ie at the end of the new shelf life). Table 2 summarises tests required for each grade of disinfectant for initial application purposes.

TABLE 2 Microbial efficacy test for disinfectants

DISINFECTANT/STERILANT COMMON NAME	APPROPRIATE TEST
Hospital grade disinfectant	Bactericidal with/without soil, extra tests for other claims as appropriate
Household/commercial grade disinfectant	Bactericidal without organic soil, extra tests for other claims as appropriate
Surface sprays disinfectant	Bactericidal carrier test, with/without soil, extra tests for other claims as appropriate
Disinfectant impregnated cloths, single and multiple use	Bactericidal, simulated in-use, extra tests for other claims as appropriate

3.15 Toxicity information

This information is required to ensure that both the patient and the user are protected from undue hazards.

Data that has been prepared for other purposes will be accepted for evaluation where the information requirements are common with those of the TGA. A copy of the full report produced by the National Occupational Health and Safety Commission for a full notification under the national Industrial Chemicals Notification and Assessment Scheme (NICNAS), for example, would generally be acceptable to satisfy the toxicology data requirements for a new chemical entity.

For detailed requirements applicants are referred to Appendix C, *Guidelines for Providing Toxicity Data for Disinfectants and Sterilants*.

GUIDELINES FOR SUBMITTING DATA SUPPORTING THE MICROBIAL EFFICACY OF DISINFECTANTS

The following information has been prepared to guide applicants in the content of data submissions to the TGA in support of microbial efficacy of their disinfectant products. Applicants should be mindful of the importance of the interrelationship between a well standardised quality product (batch to batch variation of the product must always be within agreed limits) and the microbial efficacy predicted for the product.

Enquiries concerning the content of these guidelines should be directed to the TGA Microbiologists.

Applicants should note that clear indexing and organisation of the submission will facilitate the evaluation process. The submission is required in English. This includes all test methodology and results. A summary of tests and results in English as a substitute is not acceptable.

Definitions

Minimum Effective Concentration (MEC): The minimum concentration of a biocide product which achieves the claimed microbicidal activity. The MEC is determined by dose response testing.

Minimum Recommended Concentration (MRC): The minimum concentration of a biocide product at which efficacy has been demonstrated, as recommended on the label. The MRC is not necessarily an MEC as determined by dose response testing.

Requirements

- A.1 All tests should be carried out by a GMP licensed laboratory or laboratory accredited to ISO/IEC 17025 or equivalent eg. NATA, TGA, US FDA, PIC/S, US EPA, NAMAS UK etc. A photocopy of current certification and terms of registration (i.e. accredited tests or other acceptable evidence such as a certificate of GLP) shall be included in the application. Data sourced from non accredited laboratories will only be accepted in relation to testing conducted using blood borne viruses, specifically HIV and Hepatitis B & C.
- A.2 If the product is for single use only Whether the product is used undiluted or diluted by the user to the MRC, the product should be formulated at the lower extreme of ingredient specification, stored to expiration and then subjected to the microbial efficacy tests.

The product may be tested before the end of the shelf life to initially provide a full set of data for evaluation purposes if product stored to the end of the expiration period is not available. This data should preferably be generated from more than one batch of product. Testing at the end of the shelf life will then need to be performed according to the microbiological stability requirements specified in Appendix C when product stored to the end of the expiration period becomes available. This data should also preferably be generated from more than one batch of product.

A common approach in developing a worst case product for testing is to use accelerated life testing to predict the final level of actives. These levels (with a safety factor) are then used

in the formulation of a sample for efficacy testing. However some products are unstable at elevated temperatures and may not be suitable for accelerated stability testing. Real time stability studies are preferred.

Data from all tests specified for each grade and level is not required for monitoring of stability (see Appendix C, Table 6, for the appropriate tests to be used to generate stability data). Tests must be carried out at the pH, temperature and time recommended on the label for the use, or each level of use when there is more than one level.

- A.3 Test methods must be validated. The AOAC tests are notable in this regard as, with the exception of tuberculocidal activity for Glutaraldehyde, they are validated. Where reference materials are specified in a test method, they must be used. Validation can be performed by inclusion of a reference substance, such as, benzalkonium chloride for bactericidal tests, phenol for tuberculocidal, bactericidal and fungicidal tests, 2% glutaraldehyde for sporicidal tests and possibly hypochlorite for virucidal tests.

Note: It is preferable that tests which have been validated or refereed at national or international level are used, however, whatever the situation in this regard, it is necessary for individual laboratories to validate each test method used. This should involve validation of individual operators by performance of the specified test using a control or product that is known to pass the specified test at a given concentration as well as testing to determine the most appropriate neutraliser/inactivator if necessary.

Care should be taken in the selection of reference materials. The chain length of quaternary products needs to be specified and it should be noted that one of the reference substances specified in the original reference for the AOAC Hard Surface Carrier Test is incorrect. Alkyl dimethyl benzyl-benzyl ammonium chloride should be changed to alkyl dimethyl ethyl-benzyl ammonium chloride.

The reference substances specified in the AOAC Hard Surface Carrier Test may not dissolve in water which can present problems when performing the test. In these situations, it is permissible to use commercially available disinfectants for validation purposes.

If a reference is used, the substance should be pure chemical grade and should be standardised where possible. Testing laboratories may choose appropriate reference substances.

A.4 Hospital grade disinfectants

- A.4.1 Bactericidal efficacy (excluding tuberculocidal) is the only mandatory requirement for a hospital grade disinfectant.

- A.4.2 This category MUST pass Option B of the TGA Disinfectant Test ie under dirty conditions (refer to TGO 54), or an equivalent test e.g. CEN tests such as EN Phase 2 Step 1 tests¹⁷. These tests will probably replace the Dutch 5-5-5 Suspension Test¹⁸ and the AFNOR test¹⁹, which are acceptable alternatives in the meantime provided they are modified with regard to soil.

If the disinfectant is clearly labelled for use on a precleaned surface, Option A of the TGA Disinfectant Test may be used.

- A.4.3 This category MUST pass a bactericidal carrier test. The AOAC HSCT (60 carriers per

organism) or equivalent method may be used but other tests such as CEN Phase 2 Step 2¹⁷ may also be acceptable. If additional claims regarding organisms not included in the original test are to be made ie “Kills E.coli 0157” the extra organism can be tested using 10 carriers rather than 60. Soil should be included at a minimum of 5% blood serum and inorganic soil such as hard water at a minimum of 340ppm. If the Use Dilution Test is chosen, the disinfectant passes, when there is no growth in 59 out of 60 carriers per organism. If the Hard Surface Carrier Test is used, the requirements for pass or fail are as described in the test (if 10 carriers are used for additional claims, no carriers may show growth). This may change when the results of the recent HSCT collaborative study are released. The study involved the use of hard water and inorganic soil. The results are still being collated and analysed. If Option A of the TGA Test is used for the suspension test (for products for use on precleaned surfaces), organic soil need not be included.

- A.4.4 If any specific biocidal activities (ie virucidal, fungicidal, tuberculocidal, sporicidal, or other biocidal activity) are claimed, the disinfectant must pass suitable tests with added soil (5% organic soil and inorganic soil such as hard water for that particular claim. This requirement is to apply regardless of whether Option A or Option B of the TGA test has been used. All tests should be carried out using the exposure time, temperature and pH specified on the label.
- A.4.5 For a fungicidal claim, any test of reasonable scientifically based, peer reviewed and published methodology will be considered. This includes the AOAC Fungicidal Test²⁰ which can be modified for a carrier test and the AOAC Germicidal Spray Test¹¹, which can also be modified. The CEN phases 1 and 2¹⁷ may also be acceptable, when finalised. The AFNOR test²¹ for fungicidal activity is also acceptable provided modifications in line with these guidelines are made.
- A.4.6 For a general virucidal label claim, not including blood borne viruses such as HIV, HBV and HCV, the disinfectant MUST pass tests using Poliovirus/Parvovirus and Herpes simplex as the test viruses. .
- A.4.7 The tests may be suspension tests but carrier tests are preferred. AOAC Carrier Methods that can be used as a basis are the AOAC Hard Surface Carrier Test¹⁰ and the AOAC Germicidal Spray Products Test¹¹. European Committee for Standardisation (CEN) tests or adaptations of these tests may also be acceptable when they are published/finalised. Guidance on carrier test methodology is provided in the ASTM Designation: E 1053 - 85 Standard test method for efficacy of virucidal agents intended for inanimate environmental surfaces¹². Guidance on suspension test methodology is provided in the ASTM Designation: E 1052 - 85 Standard test method for efficacy of virucidal agents intended for special applications¹².
- A.4.8 Viral recovery systems that may be used include tissue culture, embryonated egg and animal inoculation.
- A.4.9 Tests on the designated prototype viruses should be performed in quadruplicate against a recoverable viral titre of at least 4-log, which must be recovered from the test surface or suspension, and should show complete viral inactivation. If cytotoxicity is apparent, a 3-log reduction must be demonstrated beyond the cytotoxic level, and there should be complete viral inactivation. Cytotoxicity is more easily overcome in suspension tests, for which there should be 4-log reduction with complete viral inactivation. Suitable controls should be employed, which include:

- cytotoxicity controls
- disinfectant neutralisation controls
- quantitative viability control
- cell control
- carrier wash off control

A.4.10 If a label claim against HIV, Hepatitis B (HBV), Hepatitis C (HCV) or other specific virus is made, separate data must be provided, in addition to the above. Suspension tests may be used for additional specific viral claims but the recoverable viral challenge should reflect the titre found in the clinical situation. Complete viral inactivation is preferred, with a minimum 4-log reduction of specific viruses. For HIV, the method should be based on the principles described above. The use of a surrogate virus for HIV claims is not permitted at this stage. For viruses that cannot be cultured, surrogate viruses may be used. For HBV, tests with a surrogate organism such as Duck Hepatitis B Virus (DHBV) are acceptable. The electron microscope viral disruption and antigenicity tests are NOT acceptable, as they are not reliable indicators of HBV infectivity. A suitable surrogate for HCV may be Bovine Viral Diarrhoeal Virus (BVDV). Tests for HIV and HCV should be conducted against cell associated virus - a suspension test may be used if necessary. Organic soil for tests against HIV and surrogates for HBV and HCV MUST be a minimum of 50% whole blood. Other suitable references are Murray (1991)¹³, Druce (1995)¹⁴, and Lavelle (1987)¹⁵.

A.4.11 If virucidal testing is limited to lipid/enveloped viruses, such as Herpes simplex virus, a label claim for general virucidal activity will not be permitted. The label must reflect the specific viruses used for the limited testing.

A.4.12 For a tuberculocidal claim, results from a quantitative carrier test should be provided although suspension testing may be acceptable. A variety of organisms may be used, such as:

<i>M. bovis</i>	(BCG)
<i>M. tuberculosis</i>	H37RV
<i>M. terrae</i>	ATCC 15755

NOTE: *M. smegmatis* is NOT acceptable as this organism is comparatively easy to kill and its resistance patterns are substantially different from *M. bovis* etc.

A.4.13 The acceptance criterion is a 6-log reduction in test organism.

A.4.14 Suitable tuberculocidal tests include: the Ascenzi test³; the AOAC Test for Tuberculocidal Activity of Disinfectants⁴ (Note: the presumptive in vitro screening test using *M. smegmatis* is not acceptable, in addition, the confirmative in vitro test using BCG has not been validated for glutaraldehyde products); the Deutsche Gesellschaft für Hygiene und Mikrobiologie (DGHM) Carrier Test for Bactericidal, Tuberculocidal and Fungicidal Activities⁵.

A.4.15 As Europe moves towards standardisation of biocidal test methods, the DGHM test may be modified. When a standard European test method (i.e. CEN) for tuberculocidal activity is finalised, it is likely that this will also be acceptable.

A.4.16 Currently, the suspension test preferred by the TGA is the Ascenzi Suspension Test – the preferred carrier test is ASTM E 2111-00 Standard Quantitative Carrier Test Method to Evaluate the Bactericidal, Fungicidal, Mycobactericidal and Sporocidal Potencies of Liquid Chemical Germicides³⁵. Other references include Van Klingeren (1987)⁶, Best (1988)⁷, Holton (1994)⁸. Best (1994)⁹ details a method used for the analysis of five organisms, one of which is *Mycobacterium bovis*. A method similar to this is used by the Hospital Infection Research Laboratory, Birmingham, UK.

A.4.17 For a sporicidal claim, a carrier test or a suspension test may be used. The results should ideally show a 6-log reduction in spores. However, if the AOAC Sporocidal Test¹ is used, growth is allowed from two carriers or less. Other carrier tests that may be suitable are those performed by the Hospital Infection Research Laboratory at Dudley Road Hospital, Birmingham, UK² and ASTM E2111-00 Standard Quantitative Carrier Test Method to Evaluate Bactericidal, Fungicidal, Mycobactericidal and Sporocidal Potencies of Liquid Chemical Germicides³⁵.

A.5 Household/commercial grade disinfectants

A household/commercial grade disinfectant is required to:

A.5.1 Pass Option C of the TGA test (see TGO 54), or

A.5.2 Pass a suitable bactericidal carrier test, such as the AOAC HSCT¹⁰ (60 carriers per organism). Organic soil is not necessary but inorganic soil such as hard water of minimum hardness 340ppm should be included and 10 carriers for each additional bactericidal claim.

A.5.3 Pass tests as for hospital grade disinfectants where specific biocidal activities are claimed. Inorganic soil should be included (see A.4.4 – A.4.17).

A.6 Surface sprays

A surface disinfectant spray is required to:

A.6.1 Pass a bactericidal carrier test such as the AOAC Germicidal Spray Test¹¹. Sixty carriers per organism should be used and 10 carriers for each additional bactericidal claim. The performance criteria should be no growth from 59/60 carriers. Other tests of reasonable scientifically tenable design may be used, provided they can be reported at the 95% confidence level.

A.6.2 Pass the test specified in A.6.1 with added organic and inorganic soil (if the product is for dilution), if intended as a hospital grade surface spray. Organic soil should be a minimum of 5% blood serum and inorganic soil should be hard water (minimum hardness 340ppm). For products intended for use on precleaned surfaces, organic soil need not be included. A hospital grade surface spray should be tested against *Salmonella choleraesuis*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* if the AOAC Germicidal Spray Test is used. If other tests are chosen, it is expected that organisms similar to these would be used.

A.6.3 Pass the test specified in A.6.1 with added inorganic soil, if intended as a household grade surface spray that is diluted before use. A household surface spray should be tested against *Salmonella choleraesuis* and *Staphylococcus aureus* if the AOAC Germicidal Spray Test is used. If other tests are chosen, it is expected that organisms

similar to these would be used.

- A.6.4 Pass carrier tests as described in previous clauses, if specific biocidal activities are claimed. Soil should be included in these tests where the product is labelled as a hospital grade spray.

A.7 Cloth wipes (impregnated with disinfectant, for single use)

The following tests are intended to apply to products making claims of surface disinfection. They are not intended to apply to products claiming activity solely within the cloth.

A hospital grade disinfectant wipe is required to:

- A.7.1 Pass TGA Test (Option B for dirty conditions, Option A for clean conditions). This test should be conducted on the product after extraction from the wipe.
- A.7.2 Pass a simulated in-use test showing that the efficacy of the disinfectant is not reduced when combined with a cloth. Organic soil at a minimum of 5% blood serum must be included for products used under dirty conditions. The design of the test should be based on a carrier/surface test and could involve wiping the cloth over a carrier/surface and culturing both the carrier and the liquid that has been expressed from the used cloth.

Alternatively the entire cloth could be cultured. Any test of reasonable design employing these principles may be acceptable. At least 60 carriers/surfaces should be used per organism tested with 59/60 carriers showing no growth. The US EPA document “Public Health Use Antimicrobial Agent Product Performance Test Guidelines, Subseries 91A”³² can be consulted for guidance with test methodology.

- A.7.3 If specific biocidal claims are made, all claims should be supported with data from a suspension or carrier test, with added soil as appropriate. These tests should be carried out according to the requirements of A.4 *Hospital grade disinfectants*. The simulated in-use test can be carried out using the organism from the most stringent claim. This is in addition to verifying the most stringent claim with a carrier or a suspension test.

A household grade disinfectant wipe is required to:

- A.7.4 Pass the TGA Test Option C. The test should be conducted on the product after extraction from the wipe.
- A.7.5 Pass a simulated in-use test showing that the efficacy of the disinfectant is not reduced when combined with a cloth. Organic soil need not be included unless specific instructions for use on soiled surfaces are included on the label. The test method should be based on that described in A.7.2. At least 60 carriers/surfaces should be used per organism tested, with 59/60 carriers showing no growth.

A.7.6 If specific biocidal claims are made, all claims should be supported with data from a suspension or carrier test. These tests should be carried out according to the requirements of A.5 *Household/commercial grade disinfectants*. The simulated in-use test can be carried out using the organism from the most stringent test. This is in addition to verifying the most stringent claim with a carrier or a suspension test.

A.8 Cloth wipes (impregnated with disinfectant, multiple use, can include sponges impregnated with disinfectant)

Note: The following tests are intended to apply to products making claims of surface disinfection only.

A hospital grade reusable wipe is required to:

A.8.1 Pass the TGA Test using Option A or Option B as appropriate. The test should be conducted on the product after extraction from the wipe.

A.8.2 Pass a simulated in-use test after the product has been subjected to some kind of reuse protocol. Any reasonable design will be considered - a suggested method would include challenging the cloth or towelette by wiping it on a variety of surfaces. These surfaces should include periodic contamination with microbiological bioburden at a concentration of 10^6 CFU/5 mL use solution. The cloth should be allowed to dry out between uses. At the end of the use period, the product should be subjected to a simulated in-use test as described in A.7.2.

A.8.3 If extra biocidal claims are made, all claims should be supported with data from a suspension or carrier test. These tests should be carried out according to the requirements of A.4 *Hospital grade disinfectants*. The simulated in-use test can be carried out after the reuse period using the organism from the most stringent test.

A household grade reusable wipe is required to:

A.8.4 Pass TGA Test Option C. This test should be conducted on the product after extraction from the wipe.

A.8.5 Pass a simulated in-use test after the product has been subjected to some kind of reuse protocol. Any reasonable design will be considered. A suggested method would include challenging the cloth or towelette by wiping it on a variety of surfaces. These surfaces should include microbiological bioburden at a concentration of 10^6 CFU/5mL use solution. The cloth should be allowed to dry out between uses. At the end of the use period, the product should be subjected to a simulated in-use test as described in A.7.2

A.8.6 If extra biocidal claims are made, all claims should be supported with data from a suspension or carrier test. These tests should be carried out according to the requirements of A.5 *Household/commercial grade disinfectants*. The simulated in-use test can be carried out after the reuse period using organisms from the most stringent claim.

A household grade sponge (from which the active cannot be expressed) is required to:

A.8.7 Pass a simulated in-use test after the product has been subjected to some kind of reuse protocol. Any reasonable design will be considered. A suggested method would include challenging the sponge by wiping it on a variety of surfaces. These surfaces should include some kind of microbiological bioburden as described in A.8.2. The sponge should be allowed to dry out between uses. At the end of the use period, the product should be subjected to a simulated in-use test as described in A.7.2. If claims against specific bacteria are made, these organisms should be included in the test.

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GUIDELINES FOR PROVIDING TOXICITY DATA FOR DISINFECTANTS

TOXICITY

B.1 Introduction

Toxicity tests on disinfectants are necessary to identify their potential hazards. Based on the hazards identified, and the estimated exposure of patients and hospital staff to the disinfectant product, an assessment of the risks to the user and/or patient can be performed. This risk assessment forms the basis for cautionary and advisory statements on the label, designed to ensure adequate precautions are taken to protect patients and users from the identified risks.

The toxicology studies required for a disinfectant product will vary according to the nature of the proposed use and on whether the ingredients have previously been adequately characterised toxicologically.

B.2 New Chemical Entities

- B.2.1 A new chemical entity is defined as either a disinfectant active which is not included as an active in an existing disinfectant product on the ARTG, or a disinfectant excipient which is not included on either the Australian Inventory of Chemical Substances (AICS) or the ARTG.
- B.2.2 Where an existing disinfectant active is proposed to be used at a higher level of classification for the first time (eg. an application for an active from a hospital grade disinfectant to be used as an instrument grade disinfectant/sterilant), the active whilst not a new chemical entity may be considered as such with respect to the toxicology studies required, if these types of studies have not previously been assessed by the TGA.

B.3 Toxicity Data Requirements

- B.3.1 The level of toxicological detail required for a disinfectant application will depend on whether the active ingredients and excipients are existing compounds, for which adequate toxicological detail is already held by the TGA, or whether they are new chemical entities. Table 4 - *Toxicity data requirements for disinfectants and sterilants* - outlines the specific information required/recommended for each level/grade of product.
- B.3.2 Where a new disinfectant product does not contain a new chemical entity, the submission of toxicity studies is not routinely required. Sponsors are however required to hold sufficient toxicology data to demonstrate the safety of their products and this data must be made available to the TGA on request, should concern over the safety of the product arise. Sponsors may therefore consider the performance, or acquisition, of at least a limited range of toxicity studies to be prudent, in order to adequately identify the hazards to users and patients.

- B.3.3 Where a new disinfectant with specific claims contains no new chemical entity, only a limited toxicology data set, focused on the acute hazards presented by the product, is required. The information provided with an application for inclusions in the ARTG should show however, that the manufacturer has considered the broader hazards associated with the use of the product and has taken reasonable steps, in terms of formulation, labelling and product information, to ensure the product either presents minimal risk or that any hazards present are adequately described and are consistent with the nature of the product.
- B.3.4 Where a disinfectant product contains a new chemical entity a wider range of required toxicity studies is specified than that for a product based entirely on existing chemicals. The studies specified constitute a minimum data set, and sponsors should consider performing additional studies where the nature of the new chemical entity and/or the proposed use for the new product warrant them. Regardless of the data requirements specified in Table 4, sponsors are required to submit all toxicology studies available to them which might influence or have a bearing on the toxicological assessment of a new chemical. Similarly, where new data becomes available after a disinfectant product has been included on the ARTG, which might affect the toxicological assessment of one or more chemicals in that product and consequently alter the hazard profile of the product, this data is to be submitted to the TGA for consideration.
- B.3.5 Wherever possible sponsors are required to submit the full report (ie inclusive of individual animal data and full methodological details) for toxicity studies performed on a new chemical. Summary data will only be accepted where the sponsor does not have access to the original study report, with published papers for example. Some or all of the data requirements may be able to be satisfied through a competent search and review of the available literature, and provision of the relevant papers, and/or through valid scientific argument.
- B.3.6 References in Table 4 to specific methods and tests are given to assist sponsors to provide the required information. Studies conducted under equivalent study protocols from the US EPA, EEC, ICH or other widely recognised agencies/bodies are likely to be acceptable provided the key endpoints of the OECD Test Guidelines specified in Table 4 have been covered, and full methodological details are provided. Other toxicity study protocols, such as approximate lethal dose studies in lieu of LD₅₀ determinations, may also be acceptable provided dosages are sufficient to characterise acute toxicity hazards and animal numbers are adequate to provide confidence in the results presented.
- B.3.7 The sponsor has the responsibility to review and summarise the submitted toxicology data, to provide references where appropriate and to present the information requested by the TGA in a well-organised format. All papers and reports are to be submitted in the English language.
- B.3.8 Sponsors may be asked by the TGA to submit additional data, to present data in another format, or to provide more detailed explanations of the information submitted. Where a new disinfectant ingredient might reasonably be suspected to present toxicological hazards not explored through the studies included in the data sets specified in table 4, because of neurotoxicity of structurally related compounds for example, these hazards will need to be addressed either through additional studies or valid scientific argument.

B.3.9 Where a disinfectant active has previously been notified to the Chemical Assessment Division of the National Occupational Health and Safety Commission (NOHSC) under the National Industrial Chemicals Notification and Assessment Scheme (NICNAS), the data package provided to NOHSC, or the Full Report from NOHSC, may be used to satisfy those aspects of the relevant toxicology requirements in Table 4 which are common to both agencies¹.

B.4 Labelling

B.4.1 Any potential risks to the user of a disinfectant product, which may be manifested either through direct contact or through inhalation, should be clearly identified. These risks, and the steps necessary to avoid or reduce them, must be included in the labelling on the product and in the product information.

B.4.2 Labels for disinfectant products must comply with the requirements of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP), in addition to requirements specified by TGO 54.

B.4.3 New chemical entities which are also active constituents of a product are likely to be referred to the National Drugs and Poisons Schedule Committee (NDPSC) for consideration of Poisons Scheduling, First Aid Instructions, Warning Statements and Safety Directions. Sponsors should address these requirements in their submission. New chemical entities which are non active constituents, ie excipients, will only be referred to the NDPSC where they present toxicological hazards sufficient to warrant poisons scheduling.

B.4.4 Toxicity related label claims such as “non toxic”, “non hazardous” etc are inappropriate and inaccurate for disinfectant products and will not be approved. Other safety related statements such as “low irritant”, “hypo allergenic” etc, will not normally be approved but may be considered, on a case by case basis, where such information can be demonstrated to provide substantial consumer benefit. Inclusion of safety related statements on the label or consumer information of any disinfectant product covered by TGO 54, and subsequent amendments, requires the approval of the TGA. Sponsors seeking to include such statements on the product label or in the product literature will, as a minimum, need to demonstrate that the statements are;

- (a) appropriate to the intended use pattern of the product,
- (b) relevant to valid and significant consumer interests,
- (c) backed by valid scientific studies on the product in humans, and
- (d) expressed on the label accurately and informatively, for example:

“This product is of low irritancy to the skin and is hypo-allergenic to the skin as tested in normal human volunteers by XYZ laboratories.”

Table 3 Toxicity data requirements for disinfectants and sterilants^{a,i}

Study Type	OECD Test Guideline ^b	New active		New excipient ^j	New Product, containing only existing ingredients	
		High Level Instrument Grade	Other		Registrable	Listable
Acute Toxicity ^c						
Oral LD ₅₀	401, 420, 423, 425	*	*	*	*	+
Inhalational LC ₅₀	403	*	*	*	*	+
Dermal LD ₅₀	402	+	+	+	+	+
Skin irritation ^h	404	*	*	*	*	+
Eye irritation ^h	405	*	*	*	*	+
Skin sensitisation	406	*	*	*	*	+
Repeat Dose Toxicity ^d 28 to 90 day oral study	407, 408, 409, 411, 422	*	*	*		
Teratogenicity ^e						
Rat	414	*	+	+		
Rabbit		+	+	+		
Genotoxicity						
Point mutations in bacteria	471	*	*	*		
Chromosome damage in mammalian cells (<i>in vivo</i> or <i>in vitro</i>)	473, 474, 475,	*	*	*		
Other studies as necessary	Various	+	+	+		
Chronic /Carcinogenicity Study ^f	451, 453	*/+	*/+	*/+		
Occupational health monitoring studies	-	*	*	+	+	
Biocompatibility studies Cytotoxicity ^g	ISO 10993-5	*			(*)	

Notes to the table:

- * Mandatory data requirement,
- + Recommended but not mandatory
- ^a All available toxicology data which might influence the safety assessment of a new chemical must be submitted if it can reasonable be obtained by the sponsor.
- ^b OECD Test Guidelines appropriate to each study type have been specified, other internationally recognised Test Guidelines (eg those of the US EPA, ICH, US FDA), are acceptable.
- ^c Any of the alternative Test Guidelines listed against each study requirement are acceptable
- ^d A 28 day study as a minimum, but the protocol must include comprehensive histological, clinical biochemistry and haematological evaluation.
- ^e For high level disinfectants a study in at least one of the 2 preferred species is mandatory, studies in both species is preferable.
- ^f Chronic/carcinogenicity studies are only mandatory where genotoxicity studies yield clear or equivocal positive findings. For approval of an application for a product containing such a compound to be obtained, such studies would need to demonstrate an unequivocal absence of carcinogenicity at doses approaching the Maximum Tolerated Dose.
- ^g Cytotoxicity studies are required only on products used as high level instrument grade disinfectants.
- ^h Where a skin irritation study demonstrates moderate or severe skin irritancy the compound may be assumed to be a corrosive eye irritant and an eye irritation study is not then a requirement. Similarly, where adequate physico-chemical data, structure activity data or information from other sources is available (eg clinical case studies in humans), and is supplied to the TGA, to conclude that a compound is a corrosive or severe eye or skin irritant, then these studies need not be performed. In such circumstances however labelling requirements, and recommendations to the NDPSC on poisons scheduling, will be based on the more conservative classification.

- i Although human studies are not a requirement for any disinfectant product, where a sponsor wishes to make claims on a product label related to safety, eg “hypo-allergenic”, “low irritant” etc, scientifically valid studies in human volunteers will need to be provided.
- j The requirements for a product containing these ingredients will also need to be met.

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GUIDELINES FOR STABILITY TESTING OF DISINFECTANTS

C.1 Introduction

Inquiries concerning these guidelines can be directed to the Chemistry Section (sections C.1-C.3) and/or the Microbiology Section (section C.4) of TGA.

Stability studies are predictive tools used to assign a shelf life to a product. The sponsor guarantees to the user that the quality of the product will be assured provided that the labelled storage conditions are observed throughout the nominated shelf-life of the product. These guidelines describe the design, conduct, and reporting of stability studies undertaken in support of the shelf life and storage claims for sterilants and disinfectants.

These stability testing guidelines should be viewed as the **minimum requirement**. Sponsors are free to include other parameters and extend the time and scope of the study to reflect the impact of the variety of ambient temperatures and humidity conditions encountered in Australia. Besides giving valuable feedback on the chemical stability of their products, much can be learned from these studies about the suitability of the packaging to withstand harsh environmental storage conditions. Manufacturers should include several batches (minimum of two batches) in these studies to identify the effects of batch to batch variation on the shelf life prediction. The stability studies should be repeated to confirm shelf life expectations whenever there are changes to the manufacturing process, the formula or packaging.

C.1.1 Definitions

Accelerated Studies: test systems to establish the stability of a particular disinfectant or sterilant may be conducted at higher temperatures. The temperature of the studies will indicate the approximate expected shelf life in terms of Real Time and Table 4 indicates the expected correlation between temperature increase and Real Time stability outcome.

Full Battery of Tests: includes all of the microbial tests for which label claims are made as to the products capacity to perform in accordance with the requirements of TGO 54.

Minimum Effective Concentration (MEC): The minimum concentration of a biocide product which achieves the claimed microbicidal activity. The MEC is determined by dose response testing.

Minimum Recommended Concentration (MRC): The minimum concentration of a biocide product at which efficacy has been demonstrated. The MRC is not necessarily an MEC as determined by dose response testing.

Real Time Studies: stability studies on production batches may be conducted at a nominated controlled (constant) temperature where one month of study time will equate to one month of product shelf life. Studies in Real Time should be conducted in controlled conditions in the final product pack (or an identical package material).

TGO 54: means Therapeutic Goods Order Number 54 (as amended), and shall include all of the amendments to that Therapeutic Goods Order (ie TGO 54A, etc.)

C.2 Requirements

C.2.1 Overview of the stability trial

The importance of good design when planning stability studies must be emphasised

A number of principles need to be kept in mind when planning the study:

- i. Identify the key parameters which need to be monitored (see C.3.i).
- ii. Select methods of chemical analysis that are stability indicating (see C.3.ii).
- iii. Decide the duration of the study, and the time stations to be monitored during that period (see C.3.vi)
- iv. Select the storage conditions to be monitored (see C.2.2.v).
- v. The calibration, performance and reliability of climatic cabinets, incubators, refrigerators used to maintain the controlled environments should be assured before the studies are started.
- vi. Sufficient product from the batches to be monitored should be set aside to ensure that enough sample is available for analysis at each time station, with an extra amount if it is necessary to repeat and confirm unexpected results.

Conduct of the trial

- vii. Monitor all parameters at the commencement of the trial (zero time station). Do not rely on previous analyses, as the zero time information is an important reference point for the trial.
- viii. Continue to monitor each parameter as each time station occurs. Exceptional results should be confirmed and discussed.
- ix. Monitor daily the operation of each climatic cabinet, incubator, refrigerator and record the information. Values out of range should be recorded, reported, and rectified.

Reporting the trial

- x. Good records are essential for the identification of trends, and the revelation of anomalies.
- xi. The format of the reports should be decided in the planning phase eg. primary work sheets, tabulated summaries to quickly identify comparative changes.
- xii. The traceability of all records associated with the study and the author of those entries and records should be addressed.

- xiii. Periodic reviews should be undertaken during the study to assess the relevance of the design and whether the study is progressing in accordance with expectations.
- xiv. Reports should be appropriately indexed eg. batch number, trial conditions, the date that the batch was manufactured, description of the packaging, whether a pilot batch or full scale production.

C2.2 Background information

i. Formulation and Packaging

For sterilants and disinfectants, the stability, and microbial efficacy of the product should be established for each strength of the final formulation in the container to be marketed in Australia. Sponsors should confirm that the container material used does not adversely affect the stability and performance of the product. A smaller container can be substituted for a large bulky container, provided that the container used for the study is made of the same material and has a similar closure system to the market pack.

ii. Batch size

Stability testing should preferably be undertaken on full scale production batches. Where this is not possible (eg. if production has not yet commenced), laboratory (pilot) batches may be used provided they appropriately reflect the scaled-up production process

iii. Prediction of shelf life

The shelf life and maximum storage temperature nominated on the labelling should be based on full term (i.e. for the duration of the proposed shelf life) stability data. However, it is acknowledged for new products that the accumulation of stability data is a lengthy procedure and it is sometimes necessary to predict a shelf life for a product stored at a defined temperature from stability data obtained in an accelerated study conducted over a shorter period of time at an elevated storage temperature. A shelf life may be predicted from accelerated data only if the accuracy and reproducibility of the results is adequate to support the extrapolation. All data should be fully defensible. Extrapolation at various times and temperatures may be determined according to the following table (Table 5).

Table 4 - Accelerated Stability Studies Temperature/Time Correlations to Real Time

Elevated Temp ^(a) Above storage Conditions ^(b)	Time Period	Possible Shelf Life Prediction
+ 10°C	3 months	1 year
+ 15°C	3 months	18 months
+ 10°C	6 months	2 years
+ 15°C	6 months	3 years
+ 10°C	9 months	3 years

- (a) incubator temperatures shall be monitored and logged
(b) storage conditions for Australia are considered to be the temperatures of 25 - 30°C. The reference temperature used for stability testing will be that on the label.

Alternative predictive models/rules for extrapolation can be used however after proper scientific validation.

For those products evaluated by the TGA, the evaluator will assess the available data and either endorse the applicant's prediction or grant a shorter period after taking into account the chemistry, the data, and other information. No shelf life greater than 5 years is permitted.

iv. *Confirmation of predicted shelf life*

A shelf life prediction based on either an accelerated study or a stability study using laboratory/pilot batches must be corroborated by an additional real time study on regular production batches when these become available. Storage for the entire period of a real time study must be at or above the maximum temperature permitted by the labelling to maintain the rigour of the study. The use of uncontrolled temperature conditions during this period is unacceptable. Storage at “ambient temperature” or “room temperature” are not acceptable as these allow the product to be exposed to a range of conditions for different periods of time making the maximum storage temperature and likely shelf life difficult to predict. The TGA should be immediately advised if the product falls outside specification during the study.

v. *Export only products*

Products intended only for the export market need not carry an expiry date if the country of destination does not require expiry dating. If the country of destination requires expiry dating, then the studies required for products supplied in Australia shall be undertaken and a shelf life and appropriate storage warning determined. If the country of destination has other requirements in place then the testing regimen will be in accordance with those requirements.

C.3 Test methodology

- i. Sponsors should identify the key parameters applicable to the particular product. For guidance, the studies should include: appearance including colour, clarity, viscosity, phase separation. Other parameters are assay of content of the active principal, and depending on the type of product under scrutiny: acidity or alkalinity, moisture content, loss in volume, odour, change in appearance of the primary pack, evidence of deterioration of container seals, evidence of immediate container and product incompatibility (eg. the formation of a precipitate in the disinfectant solution or the formation of a coating on the walls of the container).
- ii. Chemical test methods used to measure the content of the active principals in the disinfectant should be stability indicating (that is the method must be able to distinguish between the disinfectant and any degraded disinfectant (degradation products) formed as the result of exposure to environmental factors). Sponsors should be careful of non-specific assay methods such as non-aqueous titration, titration, and some UV-VIS spectrophotometric assay methods which can have these shortcomings. Methods based on liquid or gas chromatography are more likely to be stability indicating. Sponsors should confirm by the process of method validation that the methods used are stability indicating. Full details of all test methods used in the stability studies must be provided, together with validation data where applicable. It is recognised that the active components of some products are present as complex mixtures of related compounds eg. quaternary ammonium salts. In these cases, stability testing of each of the components of the active complex may not be feasible. Where justified by the applicant, it may be acceptable to monitor the stability of a single member of the complex. The analyte chosen should be representative of the substances present in the active complex and would normally be the most unstable constituent of the mixture.
- iii. Where quantitative methods are used to determine the amount of disinfecting agent, then the results should be expressed on an absolute basis (eg. w/v, w/w), or when expressed as a percentage, then the basis of the relative measure needs to be given (eg. percentage of labelled claim). Percentages mean nothing unless they are qualified. A statement that the product complies with a particular specification or requirement is unacceptable.
- iv. Descriptive information should be full and informative.
- v. The setting of limits for content of active in the disinfectant should take into account the acceptance criteria for the performance (microbial efficacy) of the product. For guidance to sponsors, the active ingredient should remain present at or above 90.0% of the labelled claim for the duration of the proposed shelf life. For those compounds which are particularly unstable or volatile (eg. chlorine compounds), then it will be necessary for the sponsor to be able to demonstrate that the minimum active concentration (MAC) remains well above the minimum effective concentration (MEC) or minimum recommended concentration (MRC) required to pass the appropriate performance (microbial efficacy) tests for the duration of the proposed shelf life, when stored under the labelled conditions.
- vi. Testing frequency (time stations) will depend on the type of product under test. If there are signs that the product is becoming more unstable with time then periodic review (see D.2.1, 'reporting the trial') might indicate a need to reduce the interval between successive time stations. Similarly disinfectants shown to be relatively stable may have more prolonged intervals between successive time stations. For

general guidance the following regimen is suggested for real time studies: 0, 3, 6, 9, 12, 18, 24, 30, 36 months, and thereafter at six monthly intervals up to an including the proposed shelf life of the product. Sufficient time station points must be available to estimate trends. For accelerated studies, suggested testing intervals are: 0, 3, 6, 9 and 12 months but other time points eg. 1, 2, or 5 months may also be used and may be necessary for adequate accelerated studies

C.4 Microbial stability

The final formulation must pass at least one suitably sensitive test according to the appropriate TGO 54 evaluation guidelines for the level/grade of disinfectant or sterilant (see table below) at the final end point with the levels of active(s) at the final predicted level. The test should be conducted at the end of the real time shelf life, and, if there is a reuse period, at the end of this period. The microbial efficacy test for stability purposes should be monitored at the start and at the conclusion of the shelf life. Monitoring may be extended to intermediate points at the discretion of the manufacturer.

If the product is intended for single use, the testing should be performed at the minimum recommended concentration (MRC). If the disinfectant is intended for reuse, it should be subjected to a reuse protocol for the reuse period before testing and tested at the minimum effective concentration (MEC). The testing should be conducted on at least one batch at the pH and temperature specified on the label. Testing should also be conducted using the tests described in Table 6 if the shelf life is to be extended ie. At the end of the new shelf life.

TABLE 5 Microbial stability tests for disinfectants

	DISINFECTANT COMMON NAMES	APPROPRIATE TEST
1	Hospital grade disinfectant	Carrier Test (with or without soil as appropriate) with most resistant organism
2	Household/commercial grade disinfectant	TGA Test (Option C), or Carrier Test (with inorganic soil) with most resistant organism
3	Surface sprays disinfectant	Without specific claims – Bactericidal Carrier Test with most resistant organism With claims - test using most resistant organism claimed.
4	Disinfectant impregnated cloths, single and multiple use	Simulated in-use using most resistant organism claimed.

LIST OF ABBREVIATIONS

AAN	Australian Approved Name
ADG	Australian Device Group
ADI	Acceptable Daily Intake
AFNOR	Association Française de Normalisation
AOAC	Association of Official Analytical Chemists
ARTG	Australian Register of Therapeutic Goods
AS	Australian Standard
ASTM	American Society for Testing and Materials
ATCC	American Type Culture Collection
BCG	Bacille Calmette-Guérin
BVDV	Bovine Viral Diarrhoeal Virus
CAB	Conformity Assessment Branch
CEN	European Committee for Standardisation
DGHM	Deutsche Gesellschaft für Hygiene und Mikrobiologie
DHBV	Duck Hepatitis B Virus
EPA	Environment Protection Agency (US)
FDA	Food and Drug Administration (US)
GMP	Good Manufacturing Practice
GPC	Gel Permeation Chromatography
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immuno-deficiency Virus
HPLC	High Pressure Liquid Chromatography
HSCT	Hard Surface Carrier Test
MALDI	Matrix Assisted Laser Desorption Ionisation
MEC	Minimum Effective Concentration
MS	Mass Spectroscopy
MSDS	Material Safety Data Sheet
NAMAS	National Medical Accreditation Service (UK)
NATA	National Association of Testing Authorities
NCTC	National Collection of Type Cultures, London, UK
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
NMR	Nuclear Magnetic Resonance
NOHSC	National Occupational Health & Safety Commission
NOEL	No Observed Adverse Effect Level
OECD	Organisation for Economic Co-operation and Development
PIC	Pharmaceutical Inspection Convention
PIC/S	Pharmaceutical Inspection Co-operation Scheme
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TGA	Therapeutic Goods Administration (Federal)
TGAL	Therapeutic Goods Administration Laboratories Branch
TGA test	Therapeutic Goods Act (NSW) test
TGO 37 Devices	Therapeutic Goods Order No 37 - General Requirements for Labels for Therapeutic Devices
TGO 54	Therapeutic Goods Order No 54 - Standard for Disinfectants and Sterilants
UK	United Kingdom
US	United States
UV/Vis	Ultraviolet/Visible

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