SARTORIUS

Points to Consider when Validating your Sterility Testing Canisters

Sterility testing is an integral part of all pharmaceutical microbiology laboratories and is designed to detect the presence of viable microbial contaminants in sterile pharmaceuticals. Being a method based on the evaluation of microbial growth, it is crucial to distinguish between true product sterility and a false negative (Aseptic Guideline 2004). Certain ingredients used in the formulation of drugs can possess innate anti-microbial properties and prevent a sterility test from reliably reporting on the presence of viable microorganisms..

Validation is therefore performed for all new product formulations, whenever there is any change made in product formulation or if there are changes in experimental conditions. This includes selecting or making a change between a primary | secondary supplier of your sterility testing equipment. Even in the absence of a change, it is recommended to routinely revalidate all processes on a regular basis.

Sterility Testing

This involves the continual collection, evaluation and documentation of data. As a general rule, it is advisable to seek guidance and feedback from local or international regulatory bodies or advisors on the proposed methodology early in the process and prior to undertaking a validation exercise to ensure these will comply with their requirements.

There are several detailed guidelines for sterility testing, besides the pharmacopeial chapters. We have compiled the following points to be considered during the validation | revalidation of your sterility testing canisters.

Validation of Sterisart® Sterility Testing Canisters

Sterility testing canisters must be compliant with the pharmacopoeia guidelines used in the facility, and a manufacturer's validation guide should be available. Ultimately, methods validation studies should demonstrate that the method does not provide an opportunity for false negatives (Aseptic Guideline 2004). The following points should be considered when selecting or making a change to suppliers of sterility testing canisters or any other critical component
of manufacture or testing of a product.

1. Approval
This Sterility Testing Canister Validation Protocol should be reviewed by the head of Microbiology or an authorised QC microbiologist and approved by the head of Quality Assurance or their designated authority.

2. Objective
The object of this protocol is to validate Sartorius Sterisart® Canisters as approved canisters for use during quality control and lot release testing in this facility.

3. Scope
This protocol is relevant for the sterility testing team in the microbiology laboratory of the quality assurance department of the facility.

4. Reason for Validation
All critical materials and assays used in the manufacture and release of parenteral products must be validated for suitability. Validation of Sartorius Sterisart® canisters should be performed as indicated by the appropriate pharmacopoeia, regulatory guidelines, or both.

Manufacturers may want to consider validating materials and consumables from alternate suppliers for mission critical testing consumables to provide protection against process interruptions due to supply outages. These outages could be due to logistics issues, where the consumable | test item is not available locally, or if there is a failure in the manufacturing process. Examples of causes for these outages include fire, earthquake, or other natural or man-made disaster at the factory manufacturing the test consumable, lack of raw material(s) required to manufacture the test consumable, logistics issues caused by a break-down in the logistics chain due to strike action, a pandemic, or a similar interruption to freight.

5. Revalidation Criteria
Test methods should be revalidated if there is a change in manufacturing procedures, testing procedures or any of the test items, including the consumables or growth media used. The PIC/S 11.6.2.4 and the TGA guidelines on sterility testing (407) also recommends revalidating test methods every 12 months, although this is not a pharmacopoeial requirement. Revalidation may be required if a manufacturer of a consumable or media changes the construction, materials used, functionality of the consumables, or the formulation or ingredients in a media type.

6. Responsibilities
The head of Quality Assurance is responsible for approving the validation protocol, and for accepting changes to the testing procedure once equivalence of the second supply has been demonstrated. The head of the Microbiology Laboratory is responsible for overseeing the implementation of this validation protocol, and the sterility test team is responsible for performing the associated tasks. Sartorius will provide its in-house validation document. This document demonstrates that the Sterisart® canisters meet or exceed the requirements for use in a compendial sterility test in terms of the materials and methods used in their manufacture, assembly, packaging, and sterilization.

7. Reference Documents
In-house standard operating procedures that comply with relevant pharmacopoeia, cGMP and PIC/S guidelines, and any other appropriate guidelines or regulations should be referenced to perform this validation protocol. Validation experiments will be based on the current, validated work methods and SOPs in the first instance, and varied as required to achieve product validation. These internal reference documents may need updating to include any

necessary variations from the current methodology required to successfully utilize the Sterisart® canisters. Established change-management procedures for updating documents should be followed if changes are required.

8. Procedure

The following is a general overview of the procedure involved in the process of validating a sterility test, and is by no means exhaustive. Please refer to the appropriate pharmacopoeia document or local authority guidelines for a more complete description.

For new products, validation of the inactivation of product ingredients having anti-microbial activity, or rinsing them from the membrane will be required. For most re-validations of existing assays due to any of the changes listed above, existing inactivation, filtration, and rinse parameters should be suitable, but must be re-validated using bacteriostasis and fungistasis tests.

This should be performed generally by spiking the final rinse solution with <100 CFU of test organisms. In the case of products having no demonstrable anti-microbial activity, and that require no rinsing of the membrane (for example isotonic saline solutions), the product itself may need to be spiked. Growth promotion tests (positive controls) should be performed alongside sterility testing to validate the growth of test species in this assay. Bacteria should grow within 3 days and fungi within 5 days for valid results, and there should be little visible difference in microbial growth between the positive controls and the test canisters. Occasionally, there are regional differences in recommendations and practices. For instance, the TGA guideline specifies that growth promotion tests should be performed after 14 days on un-spiked sterility test samples to show the media are still capable of supporting growth. Bacteria should grow within 3 days and fungi within 5 days for valid results.

Growth promotion tests (positive controls) will require three canister sets for confirming the growth rates and patterns of the six standard species in the assay being validated, and bacteriostasis and fungistasis tests will require three canister sets per batch of product tested. Negative controls (one canister set) and negative product controls (one canister set per product) should also be conducted. While a definitive number of batches of product are no longer specified for assay validation, regulators expect manufacturers to use a science-based approach to determine how many batches will be used during validation or revalidation, and to have sound rationale for this decision. Consequently, a typical validation experiment will consist of eight or more canister sets as defined in Table 1.

Negative product controls should have all filtration and rinse steps performed apart from the actual product filtration, which is substituted by product or simulated product of known or undoubted sterility. Negative product controls should be exposed to a terminal sterilisation process, such as exposure to steam sterilisation, gamma-irradiation etc., and be packaged in a similar manner to the test sample. Alternatively, distilled water in the same or similar container could be used. Growth results of all canisters should be recorded as pass | fail. Photographic records are desirable. Where necessary, inactivation and rinse steps may need to be re-optimised to achieve the desired growth results in the bacteriostasis | fungistasis tests. These should be recorded as deviations from the existing test method.
In urgent situations, concurrent validation of alternative sterility test canisters can be performed as part of routine testing.

Canister set	Contents	TSB inoculum	FTM inoculum
1	Growth promotion assay (positive control)	*Bacillus subtilis*	*Clostridium sporogenes*
2	Growth promotion assay (positive control)	*Candida albicans*	*Staphylococcus aureus*
3	Growth promotion assay (positive control)	*Aspergillus niger*	*Pseudomonas aeruginosa*
4	Bacteriostasis	fungistasis test (per batch)	*Aspergillus niger*	*Clostridium sporogenes*
5	Bacteriostasis	fungistasis test (per batch)	*Candida albicans*	*Staphylococcus aureus*
6	Bacteriostasis	fungistasis test (per batch)	*Aspergillus niger*	*Pseudomonas aeruginosa*
7	Negative product control	None	None
8	Negative control	None	None

Table 1. Species inoculation scheme for sterility canister testing

Preferably, this should run alongside existing sterility tests, using consumables from the current supplier(s) to demonstrate equivalence to existing methods and consumables.

9. Deviations
Any and all deviations from the written procedure occurring during the validation activity should be recorded.
Any deviation occurring in inactivation or rinse steps due to changes required to achieve acceptable growth rates in the bacteriostasis | fungistasis tests in a revalidation should be recorded.

10. Conclusions
The conclusion should include the overall results of the validation process indicating if validation passes or fails for each product and should note any changes required to the test method for the tests to successfully pass the assessment criteria.

11. Report
A report including the raw data for each product evaluated should be attached as annexure. Data should be compiled by the operator performing the validation and should be checked by the head of Microbiology or their designated authority.

12. Report Approval
Reports should be reviewed by concerned departments and approved by the head of Quality Assurance or their designated authority. Report approval shows that the validation was completed successfully and according to the validation protocol.

References

U.S. Pharmacopeia. USP <71> Sterility Test
European Pharmacopoeia. Ph. Eur. 2.6.1 Sterility
Japanese Pharmacopoeia. JP 4.06 Sterility test
World Health Organization (WHO); 3.2 Test for sterility

TGA guidelines for sterility testing of therapeutic goods, 2006
21 CFR 610.12 – General Provisions
PIC/S PI 012-2 Recommendation on Sterility Testing
FDA Aseptic Guideline (Sterile Products Produced by Aseptic Processing, 2004)

Germany
Sartorius Lab Instruments GmbH & Co. KG
Otto-Brenner-Strasse 20
37079 Goettingen
Phone +49 551 308 0

USA
Sartorius Corporation
565 Johnson Avenue
Bohemia, NY 11716
Phone +1 631 254 4249
Toll-free +1 800 635 2906

For further contacts, visit
www.sartorius.com