# Guidance for Industry

## Container and Closure System Integrity Testing *in Lieu* of Sterility Testing as a Component of the Stability Protocol for Sterile Products

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**U. S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Biologics Evaluation and Research**
**Center for Drug Evaluation and Research**
**Center for Devices and Radiological Health**
**Center for Veterinary Medicine**
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**Contains Nonbinding Recommendations**

# GUIDANCE FOR INDUSTRY[1]

# Container and Closure System Integrity Testing *in Lieu* of Sterility Testing as a Component of the Stability Protocol for Sterile Products

*This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.*

## I. PURPOSE AND SCOPE

This guidance document provides recommendations to you, manufacturers, for using methods other than sterility testing to confirm container and closure system integrity as a part of the stability protocol for sterile biological products, human and animal drugs, and medical devices. This guidance document finalizes the draft guidance of the same title dated January 1998 (January 28, 1998, 63 Federal Register (FR) 4272).

Manufacturers of drugs and biologics purporting to be sterile must test each batch or lot, as the case may be, to ensure that the product in question conforms to sterility requirements. 21 CFR 211.167(a); 21 CFR 610.12. Such drugs and biologics are also subject to stability testing requirements. 21 CFR 211.166. The stability testing requirements include maintaining a written testing program designed to assess stability characteristics. Manufacturers of medical devices must validate processes, including sterilization for a device purporting to be sterile. 21 CFR 820.75. Stability testing should be part of the design validation of such devices. In vitro diagnostic products for human use are required to be labeled with stability information. 21 CFR 809.10. For products labeled as sterile, we consider sterility to be a stability characteristic.

The purpose of stability testing is to provide evidence on how the quality of a substance or product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, which enables you to establish or modify recommended storage conditions, retest periods, and shelf life or dating period, as the case may be.[2] This guidance document applies only to the replacement of the sterility test with an appropriate container and closure system integrity test in the stability written testing program (referred to in this guidance

[1] This guidance document was prepared by an intercenter working group with representatives from the Center for Biologics Evaluation and Research, Center for Devices and Radiological Health, Center for Drug Evaluation and Research, and the Center for Veterinary Medicine.

[2] "Dating period" being the term used for biologics, as defined at 21 CFR 600.3(l), and "shelf life" being the term used for other drugs.

as the "stability protocol"), recommending an alternative to sterility testing for supporting the continued capability of containers to maintain sterility. The guidance document does not apply to sterility testing methods for product sterility testing prior to release, as container and closure system integrity tests cannot demonstrate a product's initial sterility.

This guidance document provides information that we recommend you consider when you propose using alternative methods to sterility testing to confirm the integrity of a container and closure system throughout the product's shelf life or dating period. The recommendations in this guidance document apply to both pre- and post-approval stability protocols for sterile biological products, human and animal drugs, including investigational and bulk drugs. For medical devices, the recommendations in this guidance document apply to stability protocols for those devices labeled as sterile.

If you currently perform sterility testing as a stability-indicating test as part of a stability protocol, you may continue to do so. If your product is approved for an alternative to sterility testing as a component of your stability protocol, this document is not intended to recommend additional testing requirements.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

## II. INTRODUCTION

Products labeled as sterile are expected to be free from viable microbial contamination throughout the product's entire shelf life or dating period. For products labeled as sterile, we consider sterility to be a stability characteristic. As a result, the stability protocol should include confirmation of continuing sterility throughout the product's shelf life or dating period. The minimum sterility testing generally performed as a component of the stability protocol for sterile products is at the initial time point (release) and final testing interval (i.e., expiration). Additional testing is often performed at appropriate intervals within this time period (e.g., annually). However, as discussed below sterility tests for the purpose of demonstrating continuing sterility have limitations, with respect to the method's reliability, accuracy, and the conclusions that may be derived from the results. Because of the limitations of sterility tests described below, sterility tests are not recommended as a component of a stability program for confirming the continued sterility throughout a product's shelf life or dating period. Alternative methods may be more reliable in confirming the integrity of the container and closure system as a component of the stability protocol for sterile products.

This guidance document does not suggest specific test methods and acceptance criteria (except for references to USP methods), nor does it provide comprehensive lists of tests. You should determine these details based on good scientific principles for each specific container and closure system taking into consideration particular product formulations and, where applicable, routes of administration.

## III. DEFINITIONS

The definitions presented here are for the purposes of this guidance only.

A *container and closure system* refers to the entirety of packaging components that together contain and protect the product.

A *packaging component* means any single part of a container and closure system. Typical components are containers (e.g., ampules, vials, bottles), container liners, closures (e.g., screw caps, stoppers), closure liners, stopper overseals, container inner seals, administration ports (e.g., on large-volume parenterals), overwraps, administration accessories, and container labels.

## IV. BACKGROUND

Sterility tests have long been used to verify that products maintain their sterility throughout the product's entire shelf life or dating period. However, sterility testing has scientific and practical limitations, which are well known. Some of these are:

1. Sterility tests will only detect viable microorganisms present at the time of the test;
2. Viable organisms present at the time of the test can only be detected if they are capable of growth in the specified culture media;
3. Sterility tests may be subject to potential interference due to adventitious microbial contamination introduced at the time of testing, resulting in false positive readings; and
4. Sterility tests are always destructive of the samples tested and do not offer the opportunity to reexamine the same samples in the event of either positive or negative findings.

Some Centers of FDA have sought to address these shortcomings and communicated the information to you in the guidance document: "Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products" (December 3, 1993, 58 FR 63996). Section V. A., page 16 of the guidance states:

> The ability of the container-closure system to maintain the integrity of its microbial barrier, and, hence, the sterility of a drug product throughout its shelf life, should be demonstrated. […] As previously stated, sterility testing at the initial time point is not considered sufficient to demonstrate the microbial integrity of a container-closure system. […].

In the Federal Register of July 10, 1996 (61 FR 36466), we published a notice regarding the final guideline entitled "Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products", prepared under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals

for Human Use (ICH Final Guideline).[3] The ICH Final Guideline is intended to provide guidance to applicants regarding the type of stability studies that should be provided in support of marketing applications for biotechnological/biological products. [4]

## V. ALTERNATIVES

Alternatives to sterility testing as part of the stability protocol, such as replacing the sterility test with container and closure system integrity testing, might include any properly validated physical or chemical container and closure system integrity test (e.g., bubble tests, pressure/vacuum decay, trace gas permeation/leak tests, dye penetration tests, seal force or electrical conductivity and capacitance tests, etc.), or microbiological container and closure system integrity tests (e.g., microbial challenge or immersion tests). Such tests may be more useful than sterility testing in demonstrating the potential for product contamination over the product's shelf life or dating period. The advantages of using such container and closure system integrity tests in lieu of sterility tests in the stability protocol for sterile products include:

1. Such alternate methods may detect a breach of the container and/or closure system prior to product contamination;
2. Some of the alternate methods used to evaluate container and closure integrity can conserve samples that may be used for other stability tests;
3. Alternative test methods may require less time than sterility test methods which require at least seven days incubation; and
4. The potential for false positive results may be reduced with some alternative test methods when compared to sterility tests.

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[3] For veterinary products, generally, see: VICH GL17, "Stability Testing of New Biotechnological/Biological Veterinary Medicinal Products," 66 FR 19177, April 13, 2001, and VICH GL3(R), "Stability Testing of New Veterinary Drug Substances and Medicinal Products (Revision)," 71 FR 19525, April 14, 2006.

[4] The ICH Final Guideline is intended to supplement the tripartite ICH guideline entitled, "Stability Testing of New Drug Substances and Products," the notice for which is published in the Federal Register of September 22, 1994 (59 FR 48754). This guideline reflects formal scientific principles for stability testing of human drugs, and provides a general indication of the information to be generated on product stability, but leaves sufficient flexibility to encompass the variety of different practical approaches required for specific scientific situations and characteristics of the materials being evaluated.

A revision of the September 22, 1994, ICH guideline with the same title (Q1A (R)) (66 FR 56332, November 7, 2001) was issued to add information to certain sections and to provide clarification to other sections. The most important changes were as follows: (1) stress testing of the drug substance was moved from the glossary to the main text; (2) the text on test procedures was made consistent with ICH guidance "Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances" (65 FR 83041, December 29, 2000)), and relevant cross-references to other ICH guidelines were introduced; (3) the text on testing frequency was amended for accelerated testing conditions; (4) storage conditions are described in more detail, and testing at low temperature and testing of aqueous liquids in semipermeable containers are specifically addressed; (5) the postapproval commitment is clearly described; and (6) the guidance was made editorially consistent. A second revision of the guideline, "Guidance for Industry Q1A (R2) Stability Testing of New Drug Substances and Products," (68 FR 65717, November 21, 2003) was issued to harmonize intermediate storage conditions for zones I and II with long-term storage conditions for zones III and IV.

Occasionally, applicants have proposed the use of a preservative effectiveness test in lieu of the appropriate sterility test for products containing antimicrobial preservatives. However, these tests only measure the effectiveness of preservatives against a panel of five different test organisms. This method cannot confirm product sterility since it does not confirm the presence or absence of contamination, but rather only demonstrates the microbiological effectiveness of the preservative system against the five test organisms in question. For these reasons, preservative effectiveness tests are not acceptable alternative tests for monitoring container and closure system integrity or for demonstrating maintenance of sterility. However, such tests are appropriate to perform as part of the stability protocol on multi-dose containers at the end of the product's shelf life or dating period, to verify antimicrobial preservative effectiveness and preservative content.

## VI. IMPLEMENTATION

When seeking to implement container and closure system integrity testing as an alternative to sterility testing as a component of the stability protocol for sterile products, we recommend that you consider the following:

1. A container and closure system integrity test may replace sterility testing in a stability program at time points other than the product sterility test prior to release;
2. Container and closure system integrity tests do not replace sterility testing methods for product sterility testing prior to release;
3. Any validated container and closure system integrity test method should be acceptable provided the method uses analytical detection techniques appropriate to the method and is compatible with the specific product being tested. A test method is adequately validated if it has been proven through scientifically accepted studies to be capable of detecting a breach in container and closure system integrity; and
4. An appropriate container and closure system integrity test should be conducted annually and at expiration, or as otherwise required by applicable regulations.

## VII. APPLICATION SUBMISSION

For new marketing applications for sterile products, we recommend that you include container and closure system integrity tests in your stability protocol. Pending new marketing applications may be amended prior to approval.

If you wish to incorporate a validated container and closure system integrity test to demonstrate the continued capability of containers to maintain sterility for an approved product,[5] you must submit the appropriate application supplement, as follows:

[5] As previously mentioned, if you currently perform sterility testing as a stability-indicating test as part of a stability protocol, you may continue to do so. Also, if your product is approved for an alternative to sterility testing as a component of your stability protocol, this document is not intended to impose additional testing requirements.

**Human drugs**: Submit methods and data labeled "Special Supplement - Changes Being Effected" for new and abbreviated new drug applications under § 314.70.

**Animal drugs**: Submit methods and data as "Supplement - Changes Being Effected" under § 514.8.

**Biological products**: Submit a supplement with proper validation data in support of the proposed change as a "Supplement - Changes Being Effected" under § 601.12.

**Medical devices**: Submit a PMA supplement with proper validation data in support of the proposed change under § 814.39.

You should include in your application supplement a discussion of what the test method evaluates and how it is applicable to microbial integrity. You should select methods that are appropriate to the product in question, and validate all test methods. Validation of particular methods should be specific to the product container and closure system or product type. Several alternative container and closure system integrity test methods exist, as described above. We encourage you to develop innovative methods of testing the integrity of specific container and closure systems.

The use of media-filled containers is generally acceptable for initial validation studies. It may be acceptable to use media-filled containers instead of product-filled containers for testing during the product's shelf life or dating period, if the product contains a material, such as a preservative, which would bias the results of the container and closure system integrity test. If you propose to use media-filled containers for some or all of the testing, you should include data in your application supplement to support this request.

If you manufacture a number of products that use the same type of container and closure system, you may validate your integrity test method using a bracketing matrix.[6] It is not necessary to perform validation studies on each product.

The number of samples to be tested should be statistically appropriate. Samples which pass container and closure system integrity testing may be further utilized in the stability testing for that specific test period or interval; however, the test should be non-destructive and the sample unaltered by the container and closure testing method itself. Samples should not, however, be tested for container and closure system integrity at one time interval (e.g., 12 months), and then stored for further stability testing at later time periods (e.g., 24 months).



[6] See ICH guidance "Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products" (68 FR 2339, January 16, 2003).