Guidance for Industry

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

DRAFT GUIDANCE - NOT FOR IMPLEMENTATION

This guidance document is being distributed for comment purposes only.

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Comments and suggestions regarding this draft document should be submitted by March 30, 1998, to Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Drive, Rm. 1-23, Rockville, MD 20857. All comments should be identified with the docket number 98D-0021. For questions regarding this draft document contact Valerie A. Butler, Center for Biologics Evaluation and Research, (HFM-17), Food and Drug Administration, 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, 301-827-6210, FAX: 301-443-4874.

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Center for Devices and Radiological Health (CDRH)
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GUIDANCE FOR INDUSTRY[1]
CONTAINER AND CLOSURE INTEGRITY TESTING *IN LIEU* OF STERILITY TESTING AS A COMPONENT OF THE STABILITY PROTOCOL FOR STERILE PRODUCTS

I. PURPOSE

The purpose of this draft guidance document is to provide information for using methods other than sterility testing to confirm container and closure integrity as a part of stability testing for sterile products. This document is intended to provide recommendations and offer alternative methods for the sterility test for sterile biological products, human and veterinary drugs, and medical devices. This document is applicable only to stability testing, a means of confirming expiration dating. This document provides information which should be considered when a manufacturer proposes using alternative methods other than sterility testing to confirm the integrity of a container and closure system throughout its dating period.

II. SCOPE

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, and enables recommended storage conditions, retest periods, and shelf life to be established. This document applies only to the replacement of the sterility test with an appropriate container and closure integrity test in the stability protocol, permitting an alternative to sterility testing for proving the continued capability of containers to maintain sterility and is not offered as a replacement for sterility testing for product release.

III. INTRODUCTION

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[1]This draft guidance document was prepared by an InterCenter working group and represents the agency's current thinking on container and closure integrity testing for sterile products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. Submit written requests for additional copies of this document to the Office of Communication, Training, and Manufacturers Assistance (HFM-40), Food and Drug Administration, 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448. Send one self-addressed adhesive label to assist that office in processing your requests. The document may also be obtained by mail by calling the CBER Voice Information System at 1-800-835-4709 or 301-827-1800 or by fax by calling the FAX Information System at 1-888-CBER-FAX or 301-827-3844. Persons with access to the INTERNET may obtain the document using the World Wide Web (WWW). Connect to CBER at "http://www.fda.gov/cber/guidelines.htm".

In accordance with 21 CFR 600.11(h) for biological products, 21 CFR 314.50(d)(1)(i)-(ii) for human drug products, 21 CFR 514.1(b)(5) for veterinary products, and 21 CFR 809 for *in vitro* diagnostic devices, (applicable only for those devices for which stability testing is required either by regulation or the device has an expiration date on the label), sterile products are required to be free from viable microbial contamination throughout the product's entire dating period. Historically, assessment of conformance to this requirement has been met by conducting sterility tests according to the methods specified in 21 CFR 610.12 (for biological products) or the United States Pharmacopeia (USP) 23 <71> (for drug products), and 21 CFR 809 (only for *in vitro* diagnostic devices or products labeled with an expiration date). Sterility testing for product release continues to be required using the methods in the requirements for 21 CFR 610.12, and the Sterility Test USP <71>, or alternate methods approved in marketing applications. Confirmation of continuing sterility is required to be part of the stability program and the minimum testing usually requested by the following Centers-- Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), Center for Veterinary Medicine (CVM), and Center for Devices and Radiological Health (CDRH)-- is at the initial time point (release) and final testing interval (i.e., expiry). Additional testing is often requested at appropriate intervals, e.g., annually, (CVM and CDRH do not have a requirement for annual testing). However, for reasons discussed below, the utility and appropriateness of conducting sterility tests for this purpose are questionable, with respect to the method's reliability, accuracy, and the conclusions which may be derived from the results. As a consequence of the limitations of sterility tests enumerated below, alternative methods available may more reliably confirm the integrity of the container and closure system in the final form. In general, this draft guidance document does not suggest specific test methods and specifications (except for references to USP methods), nor does it suggest comprehensive lists of tests. These details should be determined based on good scientific principles for each specific container closure system for particular product formulations, and routes of administrations.

IV. DEFINITIONS

The definitions presented here are not intended to supersede the definitions of container and package in FDA's biologics regulation at 21 CFR 600.3.

A *container closure system* refers to the sum of packaging components that together contain and protect the dosage form. A *packaging system* is equivalent to a container closure system. A *packaging component* means any single part of a container 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 (LVPs)), overwraps, administration accessories, and container labels. A *package* or *market package* refers to the container closure system and associated labeling and external packaging (e.g., cartons, shrink wrap, package insert) that constitutes the article provided to a pharmacist or retail customer upon purchase. It does not include external packaging used solely for the purpose of shipping such articles. *Packaging materials* may refer to packaging components or to materials of construction.

V. BACKGROUND

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

1) The statistical limitations of the sample size used for testing in any test program also apply to sterility testing;
2) Sterility tests will only detect viable microorganisms present at the time of the test;
3) Viable organisms present at the time of the test can only be detected if they are capable of growth in the specified culture media;
4) 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
5) 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.

Occasionally, applicants have proposed use of "Antimicrobial Preservatives - Effectiveness Test" USP <51> *in lieu* of the appropriate sterility test for products containing antimicrobial preservatives. However, this test only measures 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 demonstrates only the microbiological effectiveness of the preservative system against the test organisms. However, the "Antimicrobial Preservatives - Effectiveness Test" USP <51> is an appropriate test to perform on multi-dose containers at the end of the dating period.

Recent efforts to address these shortcomings have been attempted by the individual Centers of FDA in both official and unofficial formats. The joint CDER/CVM document entitled, "Guideline for Submitting Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products" published in the **Federal Register** of December 3, 1993 (58 FR 63996) 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 . . . "

Within CDER, additional testing is recommended to demonstrate the maintenance of integrity of the microbial barrier imparted by the container and closure system. These tests should be performed annually and at expiration. It is preferred that the integrity of the microbial barrier be assessed using an appropriately sensitive container and closure integrity test.

FDA published in the **Federal Register** of July 10, 1996 (61 FR 36466), the International Conference of Harmonization (ICH) final guideline entitled, "Quality of Biotechnological Products: Stability Testing of Biotechnological /Biological Products." 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. The ICH final guideline is intended to supplement the tripartite ICH guideline entitled, "Stability Testing of New Drug Substances and Products," published in the **Federal Register** of September 22, 1994 (59 FR 48754), which reflects formal scientific principles for stability testing of drugs, and provides a general indication of the information on product stability to be generated, but leaves sufficient flexibility to encompass the variety of different practical situations required for specific scientific situations and characteristics of the materials being evaluated.

Alternatives to sterility testing as part of the stability program, such as replacing the sterility test with container and closure integrity testing, might include any properly validated physical or chemical container and closure 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 integrity tests (e.g., microbial challenge or immersion tests). Such tests may more properly address the issue of the contamination potential of the product over its shelf life. The advantages of using such container and closure integrity tests *in lieu* of sterility tests in the stability program include:

1) Use of these tests may detect a breach of container and/or closure integrity which occurred at some point in the shelf life of the product, and such a breach may allow contamination of the product to occur;
2) Some of the alternate methods used to evaluate container and closure integrity can conserve samples which 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.

Consequently, the Agency has determined that it is appropriate that alternative methods for assessment of continuing sterility are accepted in the stability program for pending new product applications, investigative or unlicensed products and approved/licensed products. Manufacturers and sponsors should consider the following with regard to sterile products:

1) A container and closure integrity test may replace the 21 CFR 610.12 sterility test or USP <71> Sterility Test (or their equivalent) in a stability program at time points other than the time of initial product release time point.
2) Container and closure integrity tests do not replace USP in sterility testing methods for product release.
3) Any adequately validated container and closure integrity test method should be acceptable provided the method uses satisfactory analytical detection techniques and is compatible with the specific product being tested. A test method is adequately validated if it has been proven through scientifically valid studies to be capable of detecting a breach in container closure integrity.
4) An appropriate container and closure integrity test should be conducted annually and at expiration or as otherwise required by applicable regulations or Agency recommendations.
5) Preservative effectiveness tests are not acceptable alternative tests for monitoring container and closure integrity or for demonstrating maintenance of sterility.

VI. IMPLEMENTATION

It is recommended to include container and closure integrity tests in the stability testing protocols for sterile product license applications or premarket notifications for *in vitro* diagnostic devices.

Approved new product applications or licenses may be updated as indicated below to include properly validated container and closure integrity tests *in lieu* of sterility testing according to USP or Code of Federal Regulation methods (or equivalent).

Incorporation of alternative methods to evaluate maintenance of sterility into the stability protocol should proceed via current mechanisms available for each of the application types. Sponsors of approved new and abbreviated new drug applications may provide methods and data under 21 CFR 314.70 for human drugs, and 21 CFR 514.8(d) for veterinary drugs, labeled "Special Supplement - Changes Being Effected." Sponsors of approved product

license applications (PLAs) should submit supplements with proper validation data in support of the proposed change under 21 CFR 601.12 for biologics, labeled "Supplement - Changes Being Effected," or if applicable "Supplement - Changes Being Effected in 30 Days." New product applications or license applications may be amended prior to approval. Firms are encouraged to select methods which are appropriate to the device or product in question, and all test methods should be validated. A discussion of what the test method evaluates and how it is applicable to microbial integrity should be included in the submission. Validation of particular methods should be specific to the product container and closure system or product type. Several alternative container and closure integrity test methods exist including, for example, dye penetration tests, bubble tests, pressure/vacuum decay, trace gas permeation/leak tests, and microbial challenge tests. Development of other innovative and container-closure-specific methods is encouraged.

The number of samples to be tested should be similar to the sampling requirements provided in USP <71> Sterility Test for drugs or in 21 CFR 610.12 for biologics. Retests are permissible, but should use at least twice as many samples as tested for in "Stage I." Samples which pass container and closure 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 integrity at one time interval (e.g., 12 months), and be stored for use at later time periods (e.g., 24 months).