

Guide to Irradiation and Sterilization Validation of Single-Use Bioprocess Systems, Part 2

The Irradiation and Sterilization Subcommittee of the Bio-Process Systems Alliance

Single-use bioprocess manufacturing systems increasingly are being implemented by the biopharmaceutical industry based on their safety, time, and cost-reduction benefits. These disposable systems are used to process or contain fluids ranging from culture media, additives, and buffers, to bulk intermediates and final formulations. In many cases microbial control or sterility is required to ensure product purity and safety. Radiation sterilization is a common means of microbial control and sterilization applied to single-use systems. The standard methods for validating radiation sterilization are not widely understood in the pharmaceutical industry, which has historically relied on moist heat

(steam) for sterilization of stainless steel bioprocess systems.

The Bio-Process Systems Alliance (BPSA) is an organization of suppliers to the biopharmaceutical industry committed to facilitating implementation of single-use systems through education and the development of industry guides to best practices. Under the auspices of The Society of the Plastics Industry, Inc. (SPI), the BPSA Technology Committee established a subcommittee to develop this guide to irradiation and sterilization of single-use bioprocess components and systems.

Part 1, in *BioProcess International's* September 2007 issue, provided the guide's scope, purpose, and background and explained the basics of gamma irradiation, microbial control and sterilization, and bioburden control of single-use systems in biopharmaceutical manufacturing. Part 2 concludes by highlighting current standards for sterilization validation, approaches to validation of single-use bioprocess systems, approaches to testing of large systems, and dosimetric release. (See the "Table of Contents" and "Glossary" boxes.)

CURRENT STANDARDS FOR STERILIZATION VALIDATION

Several industry standards are used for sterilization validation of gamma irradiated health-care products. The



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ANSI/AAMI/ISO 11137:2006 standard (*Sterilization of Health Care Products — Radiation*) was published originally in 1994. It was followed by several supporting technical reports developed by ISO and AAMI. Key among those is AAMI Technical Information Report (TIR)33:2005 on *Substantiation of a Selected Sterilization Dose — Method VD_{max}* (10).

During systematic review of ISO 11137:1994 (adopted in the United States as ANSI/AAMI/ISO 11137:1994), the document was revised and divided into three parts under the general title, *Sterilization of Health Care Products — Radiation*. The three parts of ANSI/AAMI/ISO 11137:2006 are described below.

Part 1: Requirements for Development, Validation, and Routine Control of a Sterilization Process for Medical Devices specifies requirements for development, validation, process control, and routine monitoring in the radiation sterilization for health-care products. Part 1 applies to continuous

PRODUCT FOCUS: BIOPHARMACEUTICALS

PROCESS FOCUS: UPSTREAM (PRODUCTION) AND DOWNSTREAM PROCESSING

WHO SHOULD READ: PROCESS DEVELOPMENT AND MANUFACTURING

KEYWORDS: STERILIZATION, GAMMA IRRADIATION, VALIDATION, SINGLE-USE (DISPOSABLE) SYSTEMS, DOSIMETRY, BIOBURDEN

LEVEL: INTERMEDIATE

and batch-type gamma irradiators using the radionuclides ^{60}Co or ^{137}Cs , and to irradiators using a beam from an electron or X-ray generator.

Part 2: Establishing the Sterilization Dose describes methods that can be used to determine the minimum dose necessary to achieve the specified requirement for sterility, including methods to substantiate 15 or 25 kGy as the sterilization dose.

Part 3: Guidance on Dosimetric Aspects provides guidance on dosimetry for radiation sterilization of health-care products and dosimetric aspects of establishing the maximum dose (product qualification); establishing the sterilization dose; installation qualification; operational qualification; and performance qualification.

ANSI/AAMI/ISO standards describe two methodologies for sterilization validation:

- Dose setting methods (Method 1 or Method 2, ANSI/AAMI/ISO 11137), which take into account distribution and radiation resistance of product bioburden, and to a limited extent, the end-use of the product, and
- Dose substantiation methods, (VD_{max} methods), which entail experimentation designed to qualify predetermined gamma dosages as a sterilization dose (1–3).

Some of those methods' similarities include

- Application only in conjunction with a suitable quality system
- Recognition that dose control and bioburden control are two equally important aspects to sterility assurance
- Requirement for demonstration of continued effectiveness through periodic testing to verify that the established irradiation sterilization dose remains appropriate for product sterilization.

Table 1 summarizes additional similarities and differences of the various methods. Although it illustrates the main attributes of different methods, please refer to the actual ANSI/AAMI/ISO standards or AAMI TIR for comprehensive information.

Collectively, these methods provide users with a degree of flexibility in application of standards to qualify an irradiation process, in recognition that

TABLE OF CONTENTS

Because this two-part publication of the current BPSA guide has been reformatted for BPI's house style, here is the original numbered outline of its contents, for your reference.

GUIDE TO IRRADIATION AND STERILIZATION VALIDATION OF BIOPROCESS SYSTEMS

[BPI Part 1]

- 1 Introduction
- 2 Scope, Purpose, and Background
 - 2.1 Scope
 - 2.2 Purpose
 - 2.3 Background
- 3 Basics of Gamma Irradiation
- 4 Microbial Control and Sterilization
- 5 Bioburden Control of Single-Use Systems in Biopharmaceutical Manufacturing

[BPI Part 2]

- 6 Current Standards for Sterilization Validation
 - 6.1 Introduction
 - 6.2 Dose Setting Methods (ANSI/AAMI/ISO 11137 Method 1 and Method 2)
 - 6.3 Dose Substantiation Methods
- 7 Approaches to Validation of Single-Use Bioprocess Systems
 - 7.1 Master Product
 - 7.2 Equivalent Product
 - 7.3 Simulated Product
- 8 Approaches to Testing of Large Systems
 - 8.1 Bioburden and Sterility Testing of Large Systems
 - 8.2 Use of Product Packaging as the Containment Device
- 9 Dosimetric Release
- 10 Summary

Appendices

Appendix 1: Glossary (BPI Parts 1 and 2)

Appendix 2: Comparison of Standard Irradiation Sterilization Methods for Health Care Products (Part 2, Table 1)

Appendix 3: Decision Tree for Sterilization or Microbial Control (Part 2, Figure 2)

Appendix 4: References (Parts 1 and 2)

products are not all manufactured and commercialized under uniform circumstances. Users are afforded latitude to make pragmatic decisions, provided that they observe technical correctness in several key areas:

- Flexibility to qualify sterilization of elements such as individually packaged units, kits, and components
- Flexibility to qualify sterilization of the entire unit or of a part of a unit (e.g., fluid path only)
- Use of product sample size required for irradiation cycle qualification.
- Acceptable bioburden levels presterilization
- Frequency of audit testing (performed periodically to support continued use of the established sterilization dose).

Although AAMI TIR33:2005 and ANSI/AAMI/ISO 11137 standards were initially developed with a focus on the medical device industry, they also apply to bioprocess systems and components. The remainder of this guide is therefore founded on these industry standards.

DOSE-SETTING METHODS

The dose-setting methods entail experimentation that leads a manufacturer of the sterile product to a qualified minimum irradiation dose. The general approach when using this type of method is described in ANSI/AAMI/ISO 11137:2006 and comprises the following steps:

1. Determine the target SAL.
2. Obtain a specified number of products for testing from three production lots (Table 1).
3. Experimentally determine average bioburden following ANSI/AAMI/ISO 11737-1 (11–12).
4. Determine the verification dose appropriate for the bioburden.
5. Perform a dose verification study (irradiation and sterility testing).
6. Interpret results — accepting or rejecting the study.
7. Establish the minimum dose for sterilization, based on the bioburden and SAL requirements.
8. Institute periodic dose audit testing for continued effectiveness.

Dose-setting methodologies involve qualification of the dose based on the actual radiation resistance of microorganism isolated from the product. As a result, these methods provide the lowest possible dose but

Table1: Comparing standard irradiation sterilization methods for health-care products

	ISO 11137 Method 1	ISO 11137 Method 2A	ISO 11137 Method 2B	ISO 11137 Method VD _{max} (25 kGy)	ISO 11137 Method VD _{max} (15 kGy)	AAMI TIR33 Method VD _{max} (15–35 kGy)
Limit CFU/unit (average)	0.1 to 0.9 OR ≥1 up to 1,000,000	None	Low	≤1,000	≤1.5	≤0.1 up to 440,000
Qualified Sterilization Manufacturing Dose	ETE	ETE	ETE	25 kGy	15 kGy	Ranging from 15 to 35 kGy
Units for Initial Bioburden Determination	≥30 (≥10 units from three batches)	NA	NA	≥30 (≥10 units from three batches)	≥30 (≥10 units from three batches)	≥30 (≥10 units from three batches)
Units for Initial Verification Dose	100	≥280 180 units = 20 units at nine doses +100 units per verification run	≥260 160 units = 20 units at eight doses +100 units per verification run	≥10	≥10	≥10
Units for Dose Audit Bioburden	≥10	≥10 Units for routine monitoring	≥10 Units for routine monitoring	≥10	≥10	≥10
Units for Dose Audit Sterilization	100	100	100	≥10	≥10	≥10
SAL Achieved	UD(10 ⁻² to 10 ⁻⁶ range supported)	UD	UD	10 ⁻⁶	10 ⁻⁶	10 ⁻⁶

ETE = Established through experimentation; UD = user defined; NA = not applicable

require more product samples than a dose substantiation method.

DOSE SUBSTANTIATION METHODS

The ANSI/AAMI/ISO 11137–2:2006 VD_{max} methodology allows for substantiation of two preestablished irradiation sterilization dosages: 15 kGy and 25 kGy. AAMI TIR33:2005 provides the flexibility of using seven additional sterilization doses: 17.5, 20, 22.5, 27.5, 30, 32.5, and 35 kGy. The sterilization doses range from 15 kGy for bioburden up to 1.5 cfu, 25 kGy for bioburden up to 1,000 cfu, and 35 kGy for a bioburden up to 440,000 cfu. A manufacturer should maintain strict bioburden controls at every stage of its manufacturing process. Other than the additional dose set points, ANSI/AAMI/ISO 11137–2:2006 and AAMI TIR33:2005, are based on identical principles and provide essentially identical guidance.

The general approach when using the VD_{max} method comprises the following steps:

1. Obtain products for testing from three production lots.
2. Experimentally determine average bioburden. The bioburden estimate must meet the criteria for the selected VD_{max} dose.
3. Determine the verification irradiation dose appropriate for the average bioburden.
4. Perform a dose verification study (irradiation and sterility testing)
5. Interpret results — accept or reject the study.
6. Accept or reject the predetermined irradiation dose as the minimum dose for sterilization.
7. Institute periodic dose audit testing for continued effectiveness.

The VD_{max} methods substantiate an irradiation sterilization dosage to achieve an SAL of 10⁻⁶; higher SALs

(lesser assurance of sterility) are not supported currently by the method. The fixed dosages are keyed off of two inputs: bioburden number (determined experimentally) and a data-driven assumption of worst-case bioburden resistance (2). Although the choices of sterilization dose in AAMI TIR33:2005 are fixed, the sampling requirement is smaller than Method 1 and 2 of ANSI/AAMI/ISO 11137.

APPROACHES TO VALIDATION

Single-use bioprocess systems and components pose a challenge during validation testing due to their size and complexity. A large-scale system could be, for example, an assembly of a 10,000-L bag connected to several meters of tubing, high-area filter capsule(s) that could be 254 mm (10 inches) or larger, and a connector with a complex design — or perhaps a complex manifold of connectors. Thus, you should carefully plan an easy and scientifically valid approach to bioburden and sterility testing. The sample item portion (SIP), product groupings, and family approaches to testing described in the ANSI/AAMI/ISO 11137:2006 guidelines offer strategies addressing the complexity of medical-device designs and health-care products, and are also applicable to large-scale bioprocess components and systems as outlined in the sections described below.

PRODUCT GROUPINGS/FAMILIES

The simplest strategy is for three standard manufacturing lots to be sampled. These lots should not deviate from standard manufacturing conditions. Commonly, manufacturers of multiple products develop one or more product families with the intent that a single product can represent the remaining members of its family (10). This single product used to represent a product family may be designated as a “master product,” an “equivalent product,” or a “simulated product.”

Master Product: A master product is not necessarily the largest in a family. In cases where all materials and components are the same and products vary only in size or amount of materials, the master product is usually

the largest one. Depending on the materials and manufacturing processes included, a master product may be one that possesses the most component types, the greatest combination of materials, the highest filter area, the most handling during manufacture and assembly, or a combination of those factors. Ultimately, the master product is the one deemed most challenging to a sterilization process.

Equivalent Product: Equivalent products are not necessarily those that possess identical bioburden levels, because bioburden levels naturally vary between samples and sets of samples taken over time. Products can be considered equivalent if

- Bioburden estimates are about the same
- Bioburden characterization is similar, and
- Bioburden estimate results in a sterilization dose that is about the

same when using Method 1 and Method 2, or a verification dose that is about the same when using VD_{max} .

Simulated Product: A simulated product is one that contains the same materials and components of an actual product but has been fabricated for test purposes only and thus is not an actual product. This is typically fabricated to include or combine representative worst-case attributes of a product family. One example is an assembly made with an excess of tube runs to account for different tube configurations represented in aggregate by the product family. Rejected or discarded material can be used to fabricate simulated products as long as the bioburden of the resulting simulation is representative of actual products, and the composition or configuration of the simulated product does not affect the validity of the dose determination. In designing

a simulated product, care should be taken to create one that does not create an undue challenge to the laboratory personnel who perform bioburden and sterility testing.

APPROACHES TO TESTING OF LARGE SYSTEMS

Bioburden and sterility testing of bioprocess systems or components present two specific challenges. First, large articles are especially difficult to manipulate aseptically. Specific issues include introducing such large articles into a biological safety cabinet, aseptically adding and removing fluids to the test article, aseptically handling large fluid volumes required for testing, and providing incubation space for large systems. For testing the entire product (rather than the fluid path alone), the additional issue of handling its external surfaces without contaminating them must be overcome.

GLOSSARY

Aseptic: Technically, free from disease-producing microorganisms. In bioprocess applications, it refers to an operation performed in a controlled environment or with purpose-designed connectors to prevent contamination through introduction of microorganisms (may be sterile or microbially controlled).

Bioburden: Population of viable microorganisms on a product. In the context of sterilization, it should be determined immediately before sterilization. Bioburden may be described for an item in its entirety, including external surfaces, or for fluid contact surfaces only.

Bioprocess Components: Single-use disposable parts, modules, or sections of a system, which may include but not be limited to filters, membrane chromatography units, tubing, connectors, fittings, flexible bags or rigid containers, and probes.

Bioprocess System: An assemblage or combination of bioprocess components intended to facilitate the processing of pharmaceutical or biological solutions in a single-use disposable format. The system may be preassembled before a bioburden reduction/microbial control step or assembled by a user by connecting presterilized subassemblies through the use of aseptic connections.

Dosimetric Release: The determination that a product is sterile based on physical irradiation process data rather than sterility testing.

False-Positive Sterility Test Result: Test result that is incorrectly interpreted to indicate that the test article contained viable organisms and that the article was not sterile. Commonly, such a result will derive from faulty sample handling or test execution — or from an interaction between a sample and the microbial growth medium that causes the medium to become turbid.

Irradiation: Application of ionizing radiation capable of destroying microbial bioburden.

Microbial Control: Assembly of products in a controlled clean environment followed by exposure to gamma radiation. This process reduces bioburden load but does not support a “sterile” label claim.

Sample Item Portion (SIP): Defined portion of a product assembly or component.

Sterile: Free from viable microorganisms.

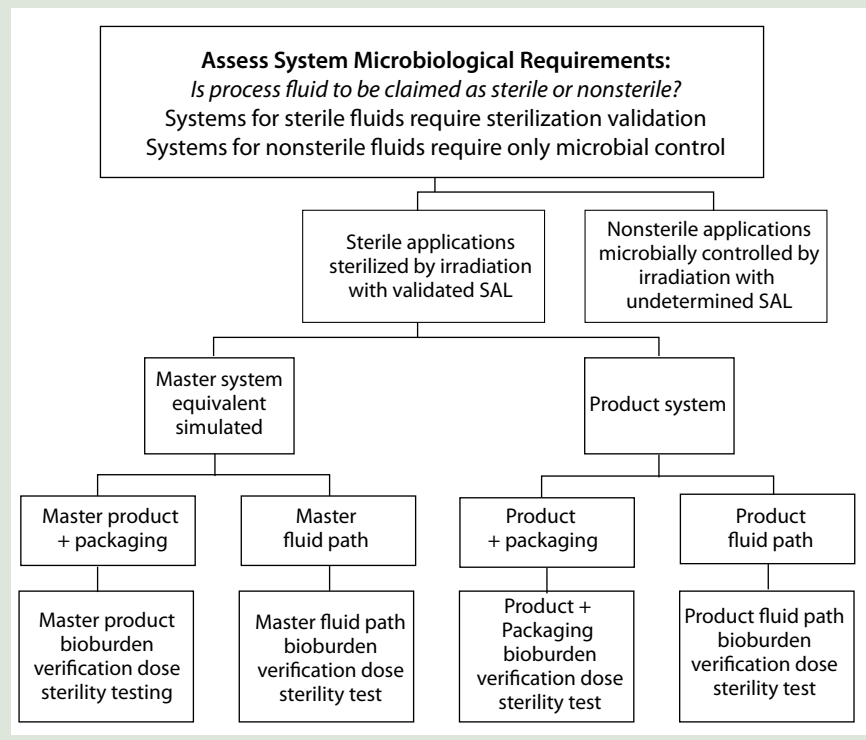
Sterility Assurance Level (SAL): In practice, the sterile state cannot be proven. Instead, sterility is expressed as the probability of a single viable microorganism occurring on an item after sterilization (1). Normally the term is expressed as 10^{-n} and not as an absolute.

Sterility Testing: Tests performed to determine whether viable microorganisms are present. Commonly, the test involves immersing a component or system or flushing a fluid pathway with sterile microbial growth medium, incubation of the medium under conditions favorable for microbial growth, and observation of turbidity or other indication of microbial growth after a suitable incubation period.

Sterilization: A validated process used to render a product free from viable microorganisms. It is generally accepted that a terminally sterilized unit purporting to be sterile attain a sterility assurance level of $\leq 10^{-6}$; that is, probability of less than or equal to one chance in one million that a viable microorganism is present in the sterilized unit (1–6). Lower SALs may be validated as sterile in some cases (2).

Validation: Establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes.

Figure 1: Decision tree for sterilization or microbial control



The second issue is that bioprocess systems or components tend to be quite expensive. Taken with the likelihood that such products are sold at very low volumes in the beginning of their life cycle, testing a relatively large number of actual articles could be prohibitive to their commercialization.

Particular approaches that manufacturers take to address these issues must be developed specific to each case because they are typically a balance between

- A desire to ensure technical correctness by testing the actual article, and
- A desire to avoid false results (inflated bioburden estimates or false-positive sterility test results) caused by handling of unwieldy articles.

Several common approaches can lessen the difficulties posed by those two issues. The following examples are intended to illustrate what may be done to overcome the issues; they are not intended to exclude other scientifically defensible approaches.

Sample Item Portion (SIP): The SIP approach allows for manufacturing and testing a reduced-scale product. This reduces both the cost of the test article and difficulties with manipulating product in the laboratory. This

approach increases experimentally determined bioburden estimates by a multiplier based on scale differences between the SIP article and the actual product represented. SIP multipliers can be determined through experimentation or simply by taking a ratio of the model to the largest system manufactured.

Fluid Path: In some cases, it is appropriate to validate the sterility of a product's fluid path. Testing the fluid path may be simpler than testing an entire product because a product acts as its own barrier to contamination. A laboratory operator has greater freedom to manipulate such products without concern for contamination.

Bioburden testing of a fluid path generally entails partially filling the product with a sterile buffer to ensure that all surfaces are wetted, then agitating the article by hand to promote suspension of organisms into the buffer. The buffer then is removed and tested for bioburden load through standard microbiological methods. As a means of better quantifying bioburden, a bioburden recovery study is performed before the actual bioburden study is initiated. The recovery study serves two purposes: quantifying the efficiency with which bioburden is recovered from the test

article and helping to define the specific methods that will be used in the actual bioburden study.

For sterility testing, the article is either partially filled with microbiological growth medium or with an extraction fluid. Following an agitation step, the growth medium can be left inside or removed and assayed for microbiological load.

Sectioning of a Large Product: To aid in handling, a large article can be split into parts that are more easily manipulated in the laboratory before testing or irradiation. This approach is especially effective if an entire product and not simply a fluid path is to be tested. One example of this approach is cutting a large biocontainer into 10 sections, dicing each into several small pieces and adding the pieces to a container that is easy to handle aseptically in a microbiology laboratory and biological safety cabinet. In this situation, each container would be tested, and the sum of the bioburden would represent the bioburden of the original bag. Similarly, all 10 containers would need to be sterile for the original biocontainer to be counted as sterile.

Use of Product Packaging As a Containment Device: Bioprocess systems or components generally are packaged in two outer bags to ensure their cleanliness and sterility. Some articles, especially those for which the entire product must be tested, are well suited to testing while they remain in their original packaging. In this scenario, the inner packaging serves as the containment vessel. A small opening is made in the packaging to access the test article and to add or remove buffer or growth medium. The opening is then aseptically sealed to maintain a closed system and prevent microbial contamination. This method is less effective for test articles that are closed-loop systems and must be opened to access internal surfaces.

DOSIMETRIC RELEASE

In qualifying a gamma irradiation microbial control or sterilization cycle, you must have the means to quantify the gamma irradiation dose. This is done through dosimetry, a field

relating to the quantification of absorbed radiation. The measurement devices are referred to as *dosimeters*. Dosimetry has specific importance in two areas of qualification:

- The verification dose used to verify a specific sterilization dosage must be measured accurately (to $\pm 10\%$)

- The load should be dose-mapped to ensure that uniformity of gamma dosage is sufficient for the configuration undergoing irradiation.

Although the science behind dosimetry is beyond the scope of this guide, various dosimetry technologies exist. Users should ensure that the dosimeter and operator are qualified to provide sufficient accuracy and precision, especially in the range of radiation dose under consideration. This method validation concept is applied as it would be to any measurement method yielding data on which product qualification and release may be based. Typically, specialized service providers of gamma irradiation perform dosimeter qualification.

After an irradiation cycle has been validated, it may be used in production of microbially controlled or sterile products. Product is released after gamma irradiation on the basis of dosimetry: a dosimetric verification that the cycle yielded a required minimum dose to the product load. No routine sterility testing is required for lot release.

Because product is released dosimetrically, its manufacturer must ensure that the dosimetry practiced by the gamma irradiation service provider is well qualified and that the gamma irradiation operation is controlled to consistently deliver the correct dose range.

MAKING MANUFACTURING DECISIONS

Disposable bioprocess systems represent a substantial benefit to biopharmaceutical process development and manufacturing. Accompanying the benefits are new decisions for all stakeholders in the adoption and incorporation of these systems. With respect to quality attributes such as microbial control and sterilization, some issues may be addressed in general terms, whereas others should be addressed in the context of a specific biopharmaceutical manufacturing process. Figure 1 provides a decision tree for sterilization and microbial control.

This guide presents a discussion of the fundamental issues related to gamma irradiation and the level of microbiological control practiced in the manufacture of disposable bioprocess systems and components. It is intended to frame the microbiological control issues and to provide a structure for making informed and rational decisions as to the level of microbiological control required in the manufacture and use of disposable bioprocess systems.

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