Product Sterility Testing … To Test or Not to Test? That Is the Question

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Abstract
The applications for sterility testing in the validation and routine control of sterilization of medical devices have changed dramatically over the years. As the definition of sterility assurance has evolved, so has the state of the science associated with product sterility testing. Historically, product sterility testing has been applied to such things as sterilization validation, sterilization lot release, packaging qualification, aseptic processing qualification, and determination of shelf life for the packaged medical device. In most of these cases, however, the results obtained from performing sterility testing on products do not provide the desired confirmation and assurance. Utilizing sterility testing on fully processed finished product is not appropriate for determination of sterilization process effectiveness, sterility assurance level, package integrity, or shelf life. The industry has developed more robust methods for validation of these applications to assure sterility and package performance. This article outlines the appropriate applications for sterility testing and highlights the applications currently in use that have significant limitations within the results and introduce undesirable risk to the validity of the data.

Product sterility testing is an essential tool of a sterilization validation or aseptic processing program. It is important to utilize product sterility testing within the proper context and not misuse data in ways that can result in inaccurate or misleading conclusions. The indications for medical product sterility testing have evolved significantly over the past few decades, along with the understanding of sterility assurance concepts. As defined in the consensus standards developed by the International Organization for Standardization (ISO), sterilization is a process used in manufacturing for which the results and effectiveness cannot be fully verified by subsequent inspection and testing of the product. The use of product sterility testing outlined by any International Pharmacopeia is not capable of determining an acceptable level of sterility assurance for an entire manufacturing batch/lot; therefore, the ISO standards do not recognize the use of product sterility testing as a routine release criteria for terminally sterilized product. This article outlines the appropriate applications for sterility testing and highlights the applications currently in use that have significant limitations and/or introduce undesirable risk to the validity of the data.

History/Evolution
Throughout the industry, there is confusion regarding the proper use of sterility testing for monitoring the effectiveness of sterilization, packaging qualification, and shelf life determination. Several decades ago, the pharmacopeial sterility test on fully processed product was acknowledged as the definitive test to determine the sterility of a batch/lot of product. However, as validation methods and principles began to be developed and understood, the pharmacopeial sterility test moved from a batch-by-batch
release–type test to a test associated with process validation. The U.S. Pharmacopeia (USP) acknowledged that the confirmation of sterility should be based on the process validation and associated data as opposed to a single limited sterility test. This was in large part due to the understanding that the sterility or sterility assurance level (SAL) of a fully processed batch/lot could not be proven using a small number of samples.

The term “sterility test” is often used generically in describing any of a number of tests that are used to determine microbial growth. Currently there are two definitions put forth by ISO/TC 198 (the ISO technical committee for the sterilization of healthcare products) associated with a sterility test in order to differentiate applications of the test (Table 1).

Table 1. Simple definitions of test methods

<table>
<thead>
<tr>
<th>Test name</th>
<th>Simple definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sterility test</td>
<td>Common name of overall test procedure</td>
</tr>
<tr>
<td>Test of sterility</td>
<td>Test procedure performed on partially processed product as part of a validation</td>
</tr>
<tr>
<td>Test for sterility (pharmacopeial test)</td>
<td>Test procedure performed on sterilized product for reference purposes or to release product after aseptic processing</td>
</tr>
</tbody>
</table>

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What Is Sterility Versus Sterility Assurance?

To understand the proper use of the sterility test in determining the effectiveness of a sterilization process, it is vital to understand the key differences between the terms “sterility” and “sterility assurance” within the context of substantiating a product label claim of “sterile” and quantifying an SAL.

Sterility is defined as the “state of being free from viable microorganisms.” Sterility is an attribute that an individual item either possesses or does not possess. Therefore, sterility testing is an attribute test that simply determines whether or not any single item possesses this characteristic.

Sterility assurance level is defined as the “probability of a single viable organism occurring on an item after sterilization.” Whereas sterility is an attribute that is either present or not, SAL is a probability that can never be reduced to zero. It also provides a useful means to accurately characterize the effectiveness of a sterilization process. The technical basis for the SAL is related to the knowledge that the rate of inactivation of a population of microorganisms by a sterilant is exponential. Therefore, by measuring microbial inactivation in a partial sterilization process, the effectiveness of the full process can be accurately measured and expressed as the probability of survival of a microorganism. This probability is expressed usually as a negative exponent (e.g., the SAL of $10^{-6}$ is the probability of a single microorganism surviving in 1,000,000 processed items).

Within the context of the definitions of sterility and sterility assurance, the appropriateness of sterility testing is defined. Sterility testing, when used as an attribute test for product subjected to a full, terminal sterilization process, provides very little information or
measurement of the effectiveness of that process—and thereby very little assurance of sterility—without testing enormous quantities of product. This is illustrated in Table 2, which identifies the SAL that is demonstrated with various sterility test sample quantities after a full sterilization process. For example, to demonstrate a typical SAL of $10^{-6}$ in a full sterilization process, a sterility test of more than one million samples would be required. Conversely, sterility testing of product after a partial (fractional) sterilization process facilitates the measurement of sterility assurance for the full process to a degree that can never be achieved by testing fully sterilized product. This approach makes it possible to demonstrate that a sterilization process is delivering a high level of assurance by sterility testing a reasonable number of samples, and explains why a compendial-based sterility test of fully processed product cannot reliably measure SALs greater than about $10^{-2}$ (i.e., a test of 100 test samples).

The Food and Drug Administration (FDA) guidance on aseptic manufacturing of drugs states in section XI.B that “sterility tests are limited in their ability to detect contamination because of the small sample size typically used. … the sterility test sampling plan only enables the detection of contamination in a lot in which 10% of the units are contaminated … if a 10,000-unit lot with a 0.1% contamination level was sterility tested using 20 units, there is a 98% chance that the batch would pass.”6 As applied to terminal sterilization, where there is a $10^{-6}$ SAL (or a one-in-a-million chance of a surviving microorganism), it is obvious that any traditional sterility test would be useless in detecting a nonsterile unit.

In addition to this significant limitation associated with testing sterilized product, there is also the uncertainty associated with the execution of sterility testing. One of the problems associated with sterility testing is contamination of the test by non–product-related microorganisms. In chapter 1211, the USP describes a typical contamination rate for sterility testing of 0.1%, or 1 per 1,000 samples.7 This level is likely to increase as the size, complexity, and manipulation of test articles increase. Thus, even if one were to attempt to test fully sterilized product using the enormous sample size required to verify a typical SAL of $10^{-6}$, the test method would almost certainly lack the necessary precision.

It is also important to note that the regulatory requirement of competent authorities worldwide to substantiate a product label claim of “sterile” is based on using a sterilization process validated to achieve a specified SAL and is not based on attribute testing of sterilized product for sterility.

In some sterilization processes such as ethylene oxide, a biological indicator (BI) process monitor containing a significant population of an organism known to be resistant to the sterilization process may be used to provide a microbial test of process acceptance. This microbial challenge is qualified during validation to be a significantly greater challenge to the process than the natural product bioburden, and is used to demonstrate the SAL.

### Inappropriate Application—When Not to Test—Limitations and Risk

Over the years, sterility testing on released finished product has been utilized in several applications that are not only inappropriate but also not valuable, due to the results having significant limitations in providing statistically valid data. The performance of sterility testing actually introduces considerable risk of contamination by the testing technique, which renders the test results questionable or invalid. There are several specific areas where sterility testing on finished product would not be appropriate, nor would it provide valuable data. One such area includes testing for sterilization

<table>
<thead>
<tr>
<th># of samples tested</th>
<th>Demonstrated (SAL)</th>
</tr>
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<tbody>
<tr>
<td>10</td>
<td>$10^{-1}$</td>
</tr>
<tr>
<td>20</td>
<td>$10^{-1.3}$</td>
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<tr>
<td>40</td>
<td>$10^{-1.6}$</td>
</tr>
<tr>
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</tr>
<tr>
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<td>$10^{-5}$</td>
</tr>
<tr>
<td>1,000,000</td>
<td>$10^{-6}$</td>
</tr>
</tbody>
</table>

Table 2. Theoretical minimum number of samples required to demonstrate sterility assurance level (SAL)
Effectiveness a) as part of final lot release, b) in evaluation of a nonconforming sterilization process for acceptance determination, and c) as regulatory surveillance. Another area is sterile barrier evaluation for package integrity testing and package shelf life determination.

Sterilization Effectiveness

Final Lot Release

The first area where product sterility testing is not appropriate is the determination of sterilization process effectiveness and compliance. As previously stated, the validation of the sterilization process is performed to demonstrate that the sterilization process will provide the required SAL for the entire product lot processed. Once the sterilization process is validated, the performance of product sterility testing as part of the measurement of the full cycle effectiveness does not provide useful data of sterility assurance and will introduce significant risk of failure due to introduction of contaminants during the performance of the test, which ultimately invalidates the test. The release of product from a routine sterilization process is primarily based on achievement of the validated sterilization process parameters. As can be seen in Table 1, the determination of the SAL of fully processed product is virtually impossible through the performance of an end-product sterility test because the number of units required for the test would exceed 1,000 just to meet the SAL of $10^{-3}$. This number of samples would be impractical and, in many cases, would consume the entire lot of product.

Nonconformance Evaluation

For the same reasons stated above, a test for sterility on product processed in a routine full cycle is also not appropriate or useful for acceptance justification for a nonconforming sterilization process. If a sterilization process results in a deviation to the process parameters or a positive growth of a routine BI monitor, testing of the product within the load would not provide any valid confirmation of SAL for the load. ANSI/AAMI/ISO 11135 indicates, "In the event of a positive BI, it is not acceptable to release product based on acceptable results of a product test for sterility." As outlined in the ISO standards, medical device sterilization is a process used in manufacturing for which the results and effectiveness cannot be fully verified by subsequent inspection and testing of the product. Because of the inherent risk of contamination during the test, a passing result of a sterility test in these cases only demonstrates the aseptic technique of the testing personnel and provides no confirmation of the sterilization process effectiveness.

Maintenance of Sterilization Process: Regulatory Surveillance

The use of sterility testing on fully processed product also provides negligible confirmation of acceptable sterility assurance programs or controls for purposes of regulatory surveillance. In some situations, sterility testing on commercially released products for the purpose of continued regulatory surveillance of the product manufacturing and sterilization programs is performed. Although this testing is well intended, product sterility testing does not provide any meaningful level of sterility assurance for product on the market but only provides assurance of sterility for the actual units tested. Therefore, these data are incapable of confirming compliance to the requirements for substantiating the product label claim of “sterile.” Since the sterilization process validation utilizes a robust challenge to confirm sterility assurance by the process, the only valuable method for assessing regulatory compliance within a surveillance program would be to confirm the continued process validation controls. In fact, the sterility testing requested by regulatory agencies on fully processed products might result in a “passing” assessment even when a sterilization process has not been appropriately validated to meet the regulatory requirements to ensure the required SAL.

In addition to not providing suitable data for sterilization process effectiveness, the product sterility testing method escalates the risk of failure due to laboratory contamination. The process of conducting a product sterility test requires removal of the product from the package and aseptically transferring the devices into a culture medium, thus inherently introducing risk of contamination during the test. Due to the level of contamination risk by even the best of laboratories, any nonsterile result would require an extensive investigation of the laboratory technique and practice as well as the storage and handling of the samples tested. For
example, a study by Odlaug et al. found that false-positive rates for sterility testing may range up to 2%.9 Because of the complexities of product sterility testing, the risk of contamination during the test presents a significant risk of failure of the sterility test, thereby resulting in a sterilization process being identified as “failed” when the process parameters meet the validated conditions and the highly resistant biological challenge (BI) results in total lethality. Therefore, the sterility testing of released, distributed product can only provide information to indicate three things: 1) only those individual devices tested are free of viable microorganisms, 2) the products tested were handled and stored so as not to damage the package and introduce a contaminant, and 3) the laboratory personnel conducting the test were able to manipulate the samples into the testing media without introducing a contaminant. Since these results are not appropriate to provide sterility assurance for the product lot and technically cannot provide a measure of the sterilization process effectiveness, the test for sterility on product processed in a routine sterilization process should not be utilized as a measure of sterilization process effectiveness.

Sterile Barrier Evaluation

Package Integrity Testing

Another area inappropriate for performing product sterility testing is in the evaluation of sterile barrier packaging. For the validation of package integrity, product sterility testing is sometimes performed on finished, sterilized product in an effort to demonstrate that the package maintained the sterile barrier. However, this type of testing actually does not provide adequate assurance of the package performance due to limitations of the test and the sterility testing method itself actually adding significant risk due to the possibility of contamination by the testing technician as previously outlined. Some of the reasons why the sterility test is not appropriate for confirming package integrity include:

1. Sterility tests will only detect viable microorganisms present on the product at the time of the test and capable of growth in the testing conditions.
2. Product sterility testing methods create significant risk of laboratory contamination.
3. The number of samples tested as part of a USP product sterility test is not sufficient to provide an appropriate attribute test for package integrity.

In review of the first reason, a failure of the package integrity would not reliably be detected through product sterility testing. Even in package integrity testing where the package is challenged with large populations of microbial organisms, microbial barrier properties cannot be assumed by an acceptable sterility test. A sterile barrier package could actually have a small breach and still demonstrate a passing result on a product sterility test, thereby giving a false “passing” conclusion for the package integrity evaluation. Since a product sterility test will only detect viable microorganisms present on the device at the time of the test, a packaging breach such as a pinhole or small tear would require a microbial event significant enough to pass through the breach, and negotiate any additional torturous pathways or packaging components, to result in a viable contaminate on the product surface capable of producing growth in the test conditions.

This failure type was demonstrated in the article published in MDDI in 1995, “In Quest of Sterile Packaging: Part I—Approaches to Package Testing.”10 A HIMA working group conducted a study where whole packaged samples with varying degrees of package integrity defects (breaches up to 3/8 in) were subjected to large populations of a test organism and then sterility tested to determine if the test was able to detect the breach in the sterile barrier. After subjecting the surfaces of the package to an indicator test organism resulting in a population range of $1.1 \times 10^3$ to $4.6 \times 10^3$ on the package surface, a sterility test was performed on the product within each package. Table 3 contains the study data summary.

As indicated in Table 3, of the 90 samples tested with known packaging defects of various sizes, only two samples demonstrated a positive (failed) sterility test result of the test organism, and one control—containing no packaging breach—resulted in growth of the indicator organism.10 Despite the packaging integrity breach, the remaining samples resulted in a “passing” sterility test, which leads to a misleading conclusion for packaging integrity performance. The publication Guidance for Industry—Container and Closure Integrity Testing
in lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products indicates that “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.”

Although the first reason gives a strong argument for not performing sterility testing as part of package integrity, another reason for not performing sterility testing is the inherent risk of contamination associated with the test method. As previously mentioned, even competent laboratories may typically have up to a 2% contamination rate for performing a product sterility test. When product sterility testing is included in a package integrity testing protocol, this risk of contamination can lead to a test result of “fail” for a package, even for a very robust package that passes all other aspects of performance testing. An example is seen in the packaging study summarized in Table 3 where a total of four test samples and one out of 30 control samples (with no breach) resulted in a false-positive growth that was not the testing indicator organism. This demonstrates the substantial level of risk associated with sterility testing that could produce an incorrect or unreliable result. Basically, the use of sterility testing can result in a “pass” result that should be “fail” or a “fail” result that should be “pass” for package integrity testing.

In addition to previous limitations and risk, the sterile barrier integrity of a package cannot be confirmed with a product sterility test with a statistically valid sample size in order to demonstrate the acceptable performance of the package. A product sterility test produces results that indicate a “growth” or “no growth” of the test samples. The USP sterility testing method that has been performed as part of package integrity testing does not provide a valid sample size for attribute testing of packaging. ASTM testing methodologies for package integrity regarding an attribute type of result require a significant number of samples to provide 95% confidence of data reliability, which would be impractical for product sterility testing applications. Due to the known limitations of product sterility testing and the fact that the number of samples is not appropriate to ensure package performance, conducting a sterility test on product cannot reliably detect a package breach or provide the number of samples needed to provide assurance of package performance.

**Shelf Life Determination**

In line with the package integrity testing, product sterility testing is also not appropriate for determination of the product shelf life. The shelf life for expiration dating of a final packaged product is not related to the sterilization process. The expiration date or shelf life of a packaged product is directly related to the stability of the product materials and the package. The sterility of the product is maintained as long as the package maintains its sterile barrier integrity. Therefore, the sterility of a product does not expire unless the packaging materials or seals deteriorate over time to allow the introduction of microbial contaminants. Since the maintenance of sterility is directly related to the integrity of the package over time, the use of a product sterility test during the accelerated aging or real-time aging process to qualify the shelf life of a packaged product has the same limitations and risk as outlined above regarding package integrity testing. A product sterility test result used for this purpose has the possibility of providing an inaccurate conclusion of package performance.

<table>
<thead>
<tr>
<th>Sample ID</th>
<th># of samples tested</th>
<th>Package defect</th>
<th>Defect size (in)</th>
<th>Positive for test organism</th>
<th>Positive for contaminant organism</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>30</td>
<td>No</td>
<td>None</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>B</td>
<td>30</td>
<td>Yes</td>
<td>3/8 × 6 × 0.005</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>C</td>
<td>30</td>
<td>Yes</td>
<td>3/16 × 6 × 0.005</td>
<td>0</td>
<td>1</td>
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<tr>
<td>D</td>
<td>30</td>
<td>Yes</td>
<td>0.010 diameter hole × 6</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

**Table 3. HIMA study summary**

Catastrophic Failure Assessment

In some instances, sterility testing has been used to confirm that a product has not experienced a catastrophic loss of sterility due to a process failure or breach of the sterile barrier during distribution. Since most such events cannot be detected by visual inspection, there is a presumption that the sterility test will determine if loss of sterility has occurred for a specified product lot. Sterility testing on a finished product sample group does not provide reliable assurance that a catastrophic loss of sterility has or has not occurred during the life cycle of the product. Again, the limitations of, and inherent risks associated with product sterility testing previously stated negate the perceived value of the results. For instance, as seen in the package integrity testing example, for product that has experienced a packaging breach, a sterility test can only detect the event if a microbial contaminant passes through the breach; however, if it does not, then the test will provide an erroneous “passing” result. Again, the sterility test on fully sterilized product cannot determine that the appropriate SAL has been achieved. Therefore, although this testing seems to provide a perceived level of confidence, the sterility test result cannot provide adequate confirmation that a catastrophic loss of sterility has or has not occurred.

Appropriate Application: When to Test

The areas where sterility testing is appropriate are associated with the validation of a process. These include a) validation of a terminal sterilization process and b) validation of an aseptic manufacturing process.

Development and Validation of a Terminal Sterilization Process

Because the inactivation of microorganisms typically follows first-order kinetics, the output of a controlled, well-defined sterilization process can be accurately measured by carrying out a sterility test after a partial process (e.g., sub-lethal, fractional, or less than a full process). The “test of sterility” within the context of validation evaluates the efficacy of the partial process at a measurable level so that an accurate SAL can be established for the routine full process.

This sterility testing for the partial process may involve the testing of BIs for sterilization processes such as ethylene oxide, moist heat, and dry heat, or it may involve actual product for those processes based on product bioburden, such as irradiation. For example, BIs of known resistance or product exposed to a partial process can be appropriately used to establish or support product sterility assurance, whereas the same testing from a complete or full process cannot establish or support an SAL.

The claim of “sterile” as defined by regulatory authorities is based on achieving a specific SAL and not on a sterility result of “pass” or “fail.” It is important to understand that a product’s “sterile” label claim is based on achieving the more stringent SAL of the entire product lot, in lieu of a simple test for sterility, which only demonstrates the sterility of the article tested as outlined in previous sections. As previously shown from Table 2, the use of a sterility test to determine process acceptability is not possible after a full sterilization process.

Validation of an Aseptic Process

Aseptic manufacturing is based upon strict controls designed to prevent microbial contamination of product during the manufacturing process. An important aspect of measuring the effectiveness of these controls is to assess the microbiological quality of product from the manufacturing process. This microbiological assessment is typically carried out by a test of sterility or test for sterility, depending on the application. This testing is typically performed by process simulation using either media fill or a final product sterility test as a measurement of aseptic conditions throughout the process.

In aseptic process validation, there are specific acceptance criteria for the number of positives based on the batch/lot size, where zero positives are allowed, with actions taken for one or more positives (see ANSI/AAMI/ISO 13408-1).\(^1\) In process validation, the number of samples tested might be in the hundreds or thousands. For this application of the sterility test, isolator technology is typically employed because of the limitations surrounding a sterility test performed in a traditional setting (i.e., not performed in an isolator). This use of the sterility test—media fill or final product testing—is acceptable because the tests can be performed in isolators or closed systems where the contamination level is in line with the acceptance criteria of the test.
In some cases, a person from a biopharmaceutical background might apply the pharmacopeial test for sterility to a batch/lot release situation, which is inappropriate for the reasons outlined herein. A sterility test performed on 20 or 40 samples from a lot/batch cannot adequately confirm the SAL of that lot/batch, and this inadequacy only increases as the batch/lot size increases. A sterility test, using media fill or product testing in a closed system, for process validation is appropriate, but a traditional sterility test for lot/batch release is not appropriate.

Summary
A product sterility test provides valuable data when appropriately used as part of process development and validation; however, a product sterility test of fully processed product cannot be used to demonstrate sterility as defined by SAL or confirmation of an acceptable sterilization program. In addition, the product sterility test is not suitable for determination of package integrity or shelf life. Because of the limitations and risks of the sterility test, the test result can be misleading in that it can result in either a false rejection or false acceptance of product or packaging, i.e., the sterility testing can result in a “pass” result that should be a “fail” or a “fail” result that should be a “pass.”

The industry international standards stipulate the specific application of sterility testing only within the scope of process validation. Therefore, there are specific indications and contraindications for the sterility test.

As seen in Table 4, the areas where a sterility test is not appropriate and should not be used are:
- Sterilization effectiveness as part of final lot release
- Evaluation of a nonconforming sterilization process for acceptance determination
- Regulatory surveillance
- Package integrity testing
- Package shelf life determination
- Determination of catastrophic failure

The areas where a product sterility test is appropriate for use are:
- Validation of a terminal sterilization process
- Maintenance of a sterilization process validation
- Validation of an aseptic manufacturing process

Conclusion
Although product sterility testing has been widely used over time to assess product for sterilization effectiveness and packaging integrity, advancements in technology and validation methods have provided more appropriate tools for qualifying these parameters. With the development of the ISO standards for sterilization and packaging, the validation methods and testing requirements outlined provide a higher assurance of sterility and package integrity for finished medical device products. The continued use of the product sterility test in inappropriate applications is unscientific in that it does not provide valid data and it carries a significant risk of reaching inaccurate or misleading conclusions.

References


Table 4. Product sterility test: when to use?

<table>
<thead>
<tr>
<th>Application</th>
<th>Test of sterility</th>
<th>Test for sterility</th>
</tr>
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<tbody>
<tr>
<td>Final lot release terminally sterilized</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Nonconformance test for release</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Regulatory surveillance</td>
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<td>Aseptic process acceptance</td>
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Note: See article sections for recommendation on when to use each test method.


