How to Investigate Sterility Test Failures

White Paper

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Introduction

The sterility test is a key microbiological test for the examination of products purportedly to be sterile. The test is used as a product release test, where the sterility of a product is defined by the absence of viable and actively multiplying microorganisms when the product is tested in specified culture media. A failure with product sterility leads to an adulterated product. The culture-based method for conducting the sterility test is clearly documented in the European and United States Pharmacopoeia. There is an emerging array of rapid and alternative methods, some of which have gained regulatory acceptance and marketing approval

Occasionally, the sterility test will produce a positive result. This event demands both an examination of the laboratory test and an examination of the production process to determine why the sterility test failure occurred. The conclusion of such an investigation will be either that the sterility test was invalid due to some type of 'laboratory error' (a position for which a great deal of caution is required given that regulatory agencies require a robust rationale) or that the product was contaminated due to some event or incident in the manufacturing or filling of the product.

When a failure happens, the immediate actions should encompass:

1. The first thing to do when being notified of a failure is to regard it as a genuine event, and not assume it to be due to laboratory error
2. A deviation needs to be opened, and senior management notified
3. There should be an SOP in place about how to conduct a microbiological contamination investigation or even a special one for a sterility test failure. This is important because such investigations are often different to a chemical test
4. The product batch should be considered non-sterile and quarantined
5. The filling line must be shutdown
6. Other products must be considered at risk - until the failed batch can be linked to a batch specific issue. A decision is required about other filling lines – here can you answer the question: "is the sterility test failure based around something specific to a certain product or line or is there a worrying breakdown with the sterility assurance system?"
7. You need an investigation team, including microbiology, production, QA, and engineering
8. The outcome must be documented and independently reviewed

This white paper examines some of the areas to consider when looking at sterility test failures, as well as outlining areas for consideration when undertaking an investigation.

Figure 1: Sterility Test Preparation (Image: Tim Sandle)

The pharmacopoeias, along with 21CFR 610.9 for biologics, allow for the adoption of alternative methods (provided that equivalence or better to the compendia method can be demonstrated). Therefore, provided that product license approval is obtained, the culture based compendial methods do not necessarily need to be followed. In terms of the different rapid and alternative sterility tests, these are grouped into tests that require amplification (growth) to show low-level contamination and those that do not. In the first group, would be technologies such as ATP bioluminescence, headspace analysis and others. Examples of the second type might be technologies such as Polymerase Chain Reaction (PCR) and vital dye/chromatography methods. Rapid and alternative sterility test methods have progressed significantly in terms of sensitivity, expediency and accuracy since the start of the twenty-first century. No single test method has emerged as the singularly superior method; furthermore, each of the commercially available technologies is not suitable for every product class. Several technologies are promising and it is possible that in the future the current compendial may no longer have the status as the referee test.

To be used as a product release test, the sterility test (culture based or rapid) requires validating. This consists of validating the media before use and the media in the presence of the product (this is to determine if the test sample will inhibit the growth of microorganisms in the test media). Each different type of product requires validating using the selected test method.

The sterility test is conducted in a controlled environment or in an isolator (the test environment is described in USP General Informational Chapter <1211> and in the PIC/S Annex to the Guide to Good Manufacturing Practice for Medicinal Products - Manufacture of Sterile Medicinal Products). Thus, the sterility test should be conducted within an EU GMP Grade A / ISO 14644 Class 5 unidirectional airflow cabinet located within an EU GMP Grade B / ISO 14644 Class 7 clean room, or in an isolator (the isolator need not be located within a controlled environment although many organisations choose to place the isolator within an ISO Class 8 area). In both the room and, most importantly the test environment, environmental monitoring should be undertaken in order to assess the cleanliness of the sterility test environment.

Although the sterility test is a mandatory product release test for sterile products, it is statistically poor at detecting anything other than gross contamination. This limitation relates to the few numbers of articles tested. Conversely, a pass result does not necessarily mean that the product is sterile. The status of sterility relates to the overall concept of sterility assurance and the methods in place to protect the product during development. With aseptically filled products, for example, it can be argued that the environmental monitoring data during the batch fill is more meaningful than the final product sterility test. For such reasons great emphasis is placed on environmental controls and a robust sterility assurance system.

Nonetheless, the sterility test is a mandatory test and over a period of time sterility test failures may occur.

When such failures occur, as with any so-termed microbiological data deviation, a documented investigation is required.

The object of such investigations is to establish the root cause, to undertake corrective and preventative actions (CAPA) and to demonstrate that the action taken is effective.

Investigation Procedure

An investigation into a sterility test failure should be conducted based on an SOP. The SOP should be one written for microbiological data deviations rather than a generic investigation procedure designed for, say, chemical analysis. The investigation must be conducted by appropriately trained and competent personnel, with an expectation that such an investigation is led by a Microbiologist. The investigation, once completed, must be properly documented and reviewed by an independent person.

Immediate Actions

Once a sterility test failure has been detected, there are some actions which should be taken immediately. The batch must be placed in quarantine and a decision taken about the status of the filling line on which the batch was filled. A documented decision should be made as to whether the line should continue to be used to fill product. At the same time, a decision should also be taken regarding other filling lines based around the question: Is the sterility test failure based around something specific to a certain product or line or is there a common breakdown with the sterility assurance system? This is something which can only be assessed based on a limited amount of initial information. These decisions may need to be re-examined as the investigation proceeds.

Common causes – things that could mean other products or lines are affected – include:

- Type of product
- Type of container
- Types of closures
- Overseals
- Filling line design and configuration
- Equipment operation
- Operators involved
- Interventions routinely and rarely performed
- Environmental monitoring history

At all times it is good practice to keep in your mind the question – What else could have been affected?

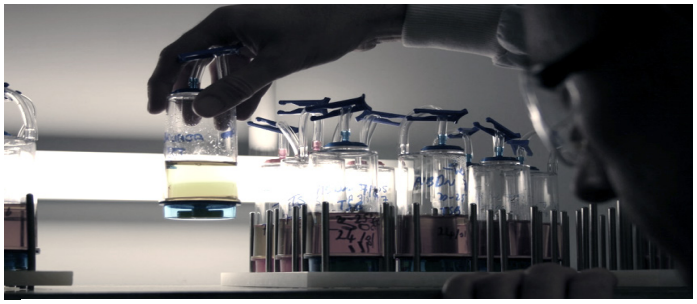

Figure 2: Reading a Sterility Testing Broth (Image: Tim Sandle)

Conducting Investigations

When conducting the investigation, a number of areas must be considered, covering both the test, test environment and the production process.

a. The sterility test and testing environment

b. The manufacturing and filling process

Figure 3: Soft-wall Sterility Testing Isolator (Image: Tim Sandle)

The examination of the manufacturing process should be based on a line of inquiry which asks: Was something different about the manufacture of the product which failed compared with other batches? To answer this, a review of the manufacturing and batch processing records, together with discussions with manufacturing staff, is required.

Laboratory Investigation

Looking at the sterility test operation first, those areas which should be examined are presented below (Sandle, 2012; Sandle, 2015). With the Microbiology laboratory investigation, records should be reviewed. These records should include:

- Description of method
- Details of the method of transfer into clean room or isolator
- Number of product units tested
- Batch / lot number
- Stage of manufacturing (e.g. finished product / intermediate / final bulk)
- Personnel performing the tests
- Dates of testing
- Test method
- Volume tested
- Diluents / solvents used
- Media batch numbers
- Temperature and incubation time
- Date of reading the test and who by
- The result (pass or fail)
- Environmental monitoring results
- Negative control results

Reviewing these areas can indicate areas of concern and this can inform the review of key areas to examine, which are:

1. **Identify the contaminant.** The identification will help with the possible points of origin (Sandle, 2011). For example:
   - A skin bacterium e.g. Staphylococcus or Micrococcus may indicate personnel activity
   - A coryneform may also suggest human activity
   - A Bacillus may suggest an environmental issue e.g. equipment transfer
   - A Gram-negative bacterium may suggest a possible water issue

   The most challenging organisms are those associated with the human skin microbiota, since these could have arisen due to a weakness with the sterility test or in relation to a control breakdown during aseptic processing.
2. **Culture media.** The culture media used in the filling operation should be examined. This will include an assessment of the type of media, consideration of who prepared the media, the growth promotion test results (sometimes described as the fertility or nutritive properties test, these are quality control tests which are performed on the media used during the sterility test to demonstrate that it is capable of supporting the growth of microorganisms), and the sterilisation records for the manufacturer of the media. If the media was externally purchased the supplier should be contacted to see if there have been any customer complaints.

   Where the media was used in the sterility test, the negative control test result should be carefully assessed. Negative controls are undertaken during the same test session as the product test samples and include the media used within the sterility test. If the negative controls recorded growth this may indicate a problem with the test environment or with the technique of the operator who conducted the sterility test. Where growth occurred in the negative controls, the contaminating microorganisms from the negative control and the failed sterility test should be carefully compared for microbial identification. This will need to take place using genotypic identification methods using technology like 16S RNA.
3. The **relative difficulty** of the sterility test procedure should be considered. Some freeze-dried products or small volume products require more manipulations and could account for contamination occurring during the sterility test due to operator manipulations (Sandle, 2004).
4. The **history** of the sterility test should be considered, especially the frequency of sterility test failures and instances where tests have been abandoned through complications. This will provide information about the reliability of the test and the testing environment and there may be patterns which emerge for certain operators. The examination should consider the results of other tests conducted that day, as well as the record for the number of failures and the number of re-tests conducted.
5. **Environmental monitoring data.** The examination of environmental monitoring data will be of great importance in making any connection of the contaminating microorganism in the sterility test to either the sterility testing environment or operator, or to the manufacturing or filling environment. Environmental monitoring should be undertaken in the dynamic state and consist of a combination of techniques, including:
   - Active air sampling
   - Settle (exposure) plates
   - Surface contact (RODAC) plates
   - Swabs or flexible films
   - Operators' gloved hand plates (Sandle, 2000)

   The assessment should include the recent environmental monitoring trends in addition to the results from the test session relating to the sterility test failure. A broader review is important because although the data from the failed sterility test session may be satisfactory, the recent trend might be indicative of a wider contamination problem.

   Environmental monitoring methods only take small samples of the environment and the methods are imprecise, so any contamination present during the sterility test session may have been missed (whereas a wider assessment of the

data might reveal a problem with environmental controls). Environmental monitoring data should be considered from both the test room and the testing environment (UDAF or isolator) and the assessment should include the disinfection and cleaning records for the room.

6. **Sterility test operator.** The history of the technician who conducted the sterility test should be carefully examined. If the technician has a good or bad recent history, may provide an indication of the possibility of contamination occurring during the sterility test. The experience of the technician is also a factor to weigh up, as is the technician's training record (for example, was the technician trained to carry out the test for the particular product?)
7. **Testing environment.** The testing environment, be it an UDAF unit with a classified cleanroom or an isolator, should be considered. The recent maintenance records should be checked in conjunction with on-going physical test data like pressure differentials, leak rates and sanitisation cycles (such as quality of the chemical agent, gassing time, dwell time etc.).

   The examination of the sanitisation cycle should include an assessment of the gassing agent, including the chemical properties.
   Also, to be considered is the aseptic transfer method and the sterility assurance relating to sterile items e.g. if waste collection tubing was autoclaved. In terms of differences between an isolator and a conventional flow cabinet, while an isolator will be more robust than an UDAF in a cleanroom, isolators occasionally can go wrong such as inadequate sanitisation, risks from leaks and problems with glove integrity.

   These factors may lead to extending out the scope of the investigation. In addition, the cleaning and maintenance records of the sterility test room and UDAF or isolator must form part of the investigation. A further factor to consider is whether any of the materials or equipment used in the sterility test required an additional sanitisation step, such as autoclaving test tubing. If so, the scope of the investigation should be extended to include the function of the decontamination unit and the load preparation.

Manufacturing Investigation

When conducting the examination of the manufacturing process, this should be based on a line of inquiry that asks: "Was there something different about the manufacture of the failed product that differs from other batches?" To answer this, it is especially important to undertake:

- A review of the manufacturing and batch processing records
- To talk with manufacturing staff

It is also important to consider if the following points can be answered:

- Are you dealing with a low number of contaminated vials and thus something more event specific?
- Are the low numbers a single event or a series of events through the process?
- Are you dealing with a gross failure and thus many contaminated vials?

A number of steps within the manufacturing process require examining. These include:

1. **Incoming raw materials:** Were the materials received satisfactory in terms of their container integrity and, most importantly, did the materials pass the microbial enumeration test and test for specified pathogens satisfactorily?
2. **Process:** The manufacturing process should be examined for any unusual events or occurrences. Were, for example, hold times for longer? In addition, were sterilisation records satisfactory? These types of questions should form the basis of the analysis.

   For the process examination, it is useful to examine the manufacturing process for unusual events. This should include a review of batch manufacturing records. With this, it can prove useful to compare 'failed' batches with 'good' batches, assessing them for anomalies like manufacturing stages that could result in contamination, such as wet equipment or opportunities for the re-contamination of clean or sterilised equipment.
3. **Intermediate process bioburden:** The test results from the intermediate process bioburden (total viable count) should be examined to determine if the microbial trend was increasing or decreasing through the process and if such variations offer a reason for an unusual build up in microbial contamination, which might relate to the sterility test failure.

   Here it is useful to ask:

   - Were the microbial counts atypical?
   - Could bioburden build-up account for the failure?
   - Are there any organisms to identify to provide possible origins?
4. **Pre-final filtration bioburden:** The most important in-process sample is the one of the bulk solution prior to final filtration near the point of use (the filling operation). Both the level of the microbial challenge (against the validated parameters for the filter) and the microbial identification should be considered.

   The review should extend to the integrity tests on the filter, pre and post use (and, where PUPSIT is required, pre-use, post-sterilisation filter integrity) to look for anomalies.

5. **Endotoxin results:** In-process endotoxin results should be examined as part of the review. Sometimes high-level endotoxin values can be recorded where total viable count results are satisfactory, indicating the presence of bacteria. The endotoxin final product test result should also be considered. A failure or high level, in conjunction with the sterility test failure, may be indicative of gross contamination and will offer a pointer towards the possible origin (such as water borne contamination through the presence of Gram-negative rods).
6. **Filling room and line:** Were the filling room and line operating to standard in terms of physical parameters and microbiological controls? Had the room passed the six-monthly HVAC tests, including particle cleanliness classification? Utility maintenance records should be examined as part of this review. Account should also be taken of any recent change controls which might impact upon the operation of the filling line.

   Changes to processing should be examined, such as assessing change controls for aspects like:

   - Recent maintenance works
   - Operational changes
   - Alterations to building design
   - New workflows
   - Alterations to personnel shift patterns
   - Alterations to filling area e.g.
     - Doors
     - Guarding
     - Belts
     - Dispensing needles
     - Stopper bowls
     - HEPA filters
7. **Filling room operations:** The filling room operations must be carefully studied, including a review of all interventions into the ISO Class 5 / Grade A zone.
8. **Operators:** The operators involved in the filling of the product should be interviewed and ideally, they should play a role in the investigation team. It is always useful to ask operators if there was anything that they can recall from the impacted process that was not recorded in the batch processing record.

   When considering the activities of operators within the filling room, the investigation should consider the number of personnel present in the room together with the names of the personnel (certain individuals may, for example, be trainees or may have a previous history with adverse trends). One factor to consider is whether the operators were fatigued as tiredness can lead to mistakes happening. When looking at each individual, an assessment should be made of the personnel related environmental monitoring for the filling operation in question and for the recent trends in association with the staff. This will include finger dabs and gowning assessments. The survey should also account for the recent media filling trial results, especially if any of the operators were associated with a media fill failure.
9. **Media fills.** Data from the most recent media fill should be analysed. This will be doubly important if the most recent media fill recorded any turbid vials. If the investigation into the fill indicates that any interventions may have been the cause, consideration should be made as to whether the interventions were included and simulated during the media fill or if there were any concerns when the intervention was simulated. In carrying out the analysis, it is useful to draw comparisons with recent media simulation trials, such as:

   - Assessing any media fill failures to determine if there is commonality of root causes
   - Checking all interventions from the sterility failure batch were undertaken in the most recent media fill – if not, the intervention types could be a point of risk
10. **Environmental monitoring:** The viable and non-viable particulate data in relation to the product fill and data relating to the background environment should be examined. This will include identification results of all microorganisms recovered. Where similar species have been recovered these should be characterised to determine if the microorganisms are related at the genetic level using genotypic testing. The results of such analysis should be related back to the microorganism(s) recovered from the sterility test failure. The review of environmental monitoring data should include both critical and non-critical areas, with a consideration of recent trends for the filling room and the process. Examine environmental monitoring data for:

    - Batch specific events
    - Longer term trends – possible gradual deterioration
    - Especially consider:
      - Personnel finger plates
      - Exit suit gown plates
    - Compare all species recovered in relation to the sterility test contaminants
    - Compare isolates to any from the sterility testing facility

    If the microorganism detected in the sterility test is rarely found in the laboratory environment, then product contamination is more likely than laboratory error. However, if the microorganism is found in both the laboratory and production environments, then it can indicate either product contamination or laboratory error.

    With environmental monitoring data review, trend data may indicate a gradual deterioration of operational conditions. This should extend to consideration of cleanroom classification data.

11. **Cleaning and disinfection:** Cleaning and disinfection records pertaining to the filling room and filling zone should be examined. Inadequate cleaning may explain why microbial contamination occurred. Such a review should consider the effectiveness of cleaning techniques and the expiry time of the detergents and disinfectants used for the cleaning on the day of the product fill.

    The microorganism isolated from the sterility test failure should be considered in terms of disinfectant efficacy, particularly whether the microorganism would be killed by the disinfectant. If there are doubts, as in the case of an isolation of a Gram-positive sporing rod, a decision should be made whether or not a disinfectant challenge test (using the suspension test method) should be undertaken to demonstrate if the microorganism is resistant to the in-use concentration of the disinfectant.

Sterility Test and Process Area Link

The key piece of information which draws together the investigation between the sterility test and the process area is the microorganism detected within the sterility test failure. The assessment as to where else the microorganism is found, in either the sterility test environment or the process area, provides important information as to the origin of the contamination. Any suggested link must be made at the genetic level. If the microorganism can be linked to the process area, then the sterility test can be confirmed. If the microorganism is linked to the sterility test area, a link cannot be automatically confirmed. Although it is a possibility, a reason for the contamination occurring during the sterility test must be made together with a robust case for making the connection. Where this occurs, the response must be to undertake a re-test.

If no link can be made then the only acceptable response to is confirm the sterility test as a genuine failure and to reject the batch.

Re-testing

The pharmacopoeias allow for a retest of the product if persuasive evidence exists to show that the cause of the initial sterility failure was induced by the laboratory. Identification and speciation of the isolate(s) is a significant contributing factor to the final decision. If the First Stage sterility test can be invalidated by the laboratory, then the pharmacopoeias allow for Second Stage sterility testing. Second Stage sterility testing requires double the original number of samples tested. The Second Stage test can be repeated if evidence exists invalidating the test due to a laboratory error as above. Most companies allow only for repeat sterility test. Under these circumstances, if the repeat sterility test fails, even if this is again attributed to testing error, no further repeat sterility tests can be undertaken – the product cannot be released.

Concluding Sterility Test Failure Investigations

At the end, you need to make a decision. Three possible outcomes:

1. The sterility test failure was a process specific event. Here the:
   - Batch is rejected
   - Status of other batches needs to be considered, including those previously released
   - Risk review is needed before any further processing
2. The sterility test failure was due to laboratory error. In these circumstances, a solid case is required for justifying a repeat sterility test and this ideally needs to be based on a genetic microorganism match.
3. If the investigation is inconclusive, you have no choice but to err towards batch rejection.

When concluding sterility test failure investigations, the investigation should lead to the establishment of a root cause or most probable root cause. This will centre upon deciding how the contamination got into the product: Was this the result of something relating to the process or to the filling of the final product, or was this a so-termed 'false positive' and the result of a contaminant transferred during the sterility test operations? Care must be taken and a robust case constructed if the investigation concludes laboratory error. Such a conclusion must be unequivocal and be based on genetic microbial identification testing at the DNA or RNA level.

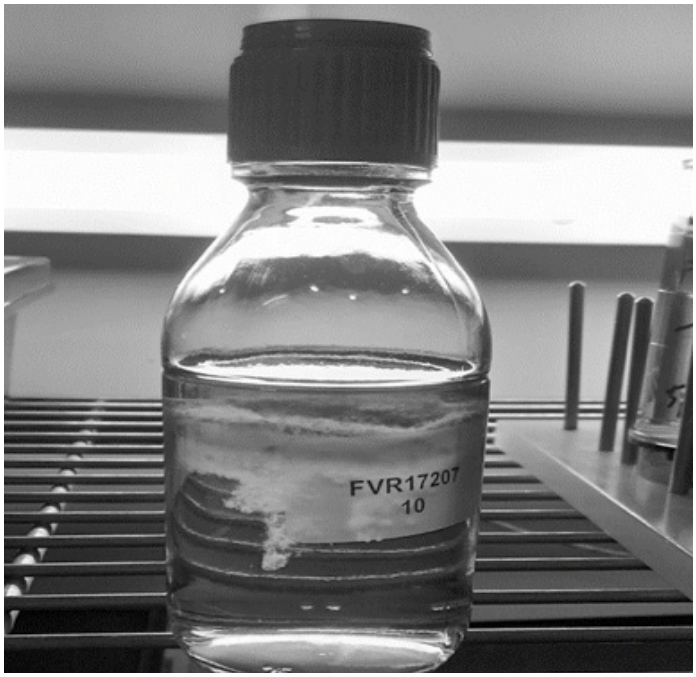

Figure 4: Sterility test bottle showing turbid growth (Image: Tim Sandle)

Figure 5: Sterility testing (Image: Tim Sandle)

It is possible that the investigation will conclude with more than one root cause. This may lead to a thorough review of processing or filling operations, together with appropriate preventative actions to prevent re-occurrence. Where the root cause is established, the pharmaceutical organisation must make decisions about batches of product already on the market as well as release considerations for batches under quarantine. This will be based around whether the root causes relate to a specific batch incident or to a wider process problem.

The documentation for the sterility test failure investigation should be detailed and cover most of the points covered in this article as well as other considerations specific to the product line. Regulatory authorities will expect logical, detailed and a well-presented investigation report.

Follow-up Actions

All sterility test failure investigation outcomes require follow-up actions.

For process failures:

- Perform a risk assessment
- Perform impact assessment for all products, processes and filling areas
- Set appropriate preventative actions
- Re-train operators
- Run at least one media fill (some companies require three media fills to be conducted where the line requires requalification)

For laboratory failures:

- Understand the control breakdown
- Assess training, sanitisation, disinfection practices etc.
- Re-train staff

Follow up actions can take the form of effectivity checks in relation to the deviation raised to examine the sterility test failure.

Summary

This white paper has outlined some best practices for conducting sterility test failure investigations, illustrating how some of these practices can be applied through the use of a case study. In doing so, the white paper has considered things to do immediately a failure occurs (beginning with the deviation report) and has then proceeded to discuss the key points for a laboratory failure investigation and the key points for a process failure investigation, together with some possible outcomes. The paper has also discussed the necessity for performing follow-up actions as a way of effectivity checks.

By way of summary, with the investigation stemming from a sterility test failure, consideration should be given to:

For process failures:

- Speciation of the organism
- Record of laboratory results and deviations
- Environmental monitoring of production environment
- Monitoring personnel
- Product pre-sterilisation bioburden
- Production record review
- Manufacturing history

Any isolates from sterility testing should be identified to species level. Here:

- The use of genotyping techniques is encouraged
- Identical methodologies should be employed in species identification in sterility test and environmental monitoring program

All investigations into sterility test failure should be documented. Where the conclusion indicates that the failure is not due to laboratory error, the focus of the investigation is upon the production process (it is good practice to have begun a process investigation at the same time as the investigation into the test).

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Dr. Tim Sandle has over twenty-five years' experience of microbiological research and biopharmaceutical processing. He is a member of several editorial boards and he has written over six hundred book chapters, peer reviewed papers and technical articles relating to microbiology. Dr. Sandle works for a pharmaceutical manufacturer in the UK, and is a visiting tutor at both the University of Manchester and UCL.

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