



TECHNICAL TIP

SCREENING FOR ADVERSE AND INHIBITORY SUBSTANCES

Test method validation for adverse and/or inhibitory substances is important to ensure that the measurement of contamination on a device is not impacted by substances present in the test.

Adverse substances and/or inhibitory substances (e.g. antimicrobial substances) of a product can influence the determination of bioburden levels or the tests of sterility. It is important to provide information to the test laboratory about such substances before laboratory tests are performed.

Origination of Adverse and/or Inhibitory Substances:

1. There may be substances present on or in the product that impart antimicrobial properties as part of the device design. Examples of this would be antibiotics, batteries, coatings, wound dressings impregnated with silver, or other metals.

In these cases, the presence of substances is known by the device design team/manufacturer prior to sending to the test laboratory and subsequent test method development. Advanced notification of information on known adverse and/or inhibitory substances will allow the test laboratory to carry out feasibility work and build neutralization into the proposed test methods in advance of beginning the method validations. Sharing this information with the test laboratory along with Safety Data sheets (SDS) will ensure that appropriate safety and disposal processes are considered as part of initial product/method review.

2. There may be adverse and/or inhibitory substances present on/in the product that unintentionally cause inhibition in the test method. Examples of this may be product coatings or residual detergents from cleaning processes.

Typically, the presence of these substances or their impact is unknown by the manufacturer or test laboratory prior to test method development and is only discovered during the first phase of testing. They are often more difficult to overcome as the cause of the inhibition may not be obvious and additional method development work may be required to resolve the inhibition. Testing for these unknown adverse

and/or inhibitory substances may help avoid delays to project timelines.

ISO 11737-1 and ISO 11737-2 state that if the physical or chemical nature of product to be tested is such that substances might be present or released and therefore could adversely affect the multiplication of microorganisms, a system to neutralize, remove, or, if this is not possible, minimize the effect of any such substances shall be used. The effectiveness of such a system shall be demonstrated.

For bioburden tests, it is important to demonstrate that the product does not prevent the growth or detection of microorganisms and thus create a falsely low measurement of contamination on a device. The bioburden method recovery efficiency can be a good parameter for assessing the presence of adverse or inhibitory substances (see Tech Tip for Bioburden Method Validation for more information).

It is also possible to determine the presence or absence of inhibitory effects of the product on microbial growth by screening different microorganisms and not only the typical spore-forming microorganism used for method validation. The same test methods for extraction and culturing should be employed for the adverse screening and routine bioburden monitoring (including the recovery efficiency validated during the bioburden method validation).

What Options are Available to Minimize Effect of Adverse and/or Inhibitory Substances?

- Reduction of the concentration of inhibitory substances by dilution
- Appropriate inactivation procedures
- Appropriate neutralization procedures

For test of sterility, the occurrence of false negative results may influence the interpretation of the data obtained during validation by overestimating the effectiveness of sterilant treatment. The presence of microbicidal and/or microbiostatic substances

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released from the product during sterility testing could influence the occurrence of false negatives. Therefore, a sterility method suitability test (also referred as a bacteriostasis/fungistasis test) must be performed to detect the presence of substances that inhibit the proliferation of microorganisms in a test of sterility.

The product being tested should be screened to determine if any inhibitory substances are released into the medium that could cause falsely negative (no growth) sterility test results. The sterility method suitability is performed by inoculating low numbers of representative microorganisms into the liquid medium containing a product.

What Options are Available to Minimize Effect of Adverse and/or Inhibitory Substances?

- Addition of neutralizer(s) to the growth medium or eluent
- Removal of substance from an eluate by filtration
- Reduction of the concentration of substance to an ineffective level by dilution
 - NOTE: Dilution of the test may be achieved by increasing the volume of growth medium or eluent and, where necessary, subdividing the product into a number of test containers

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