TECHNICAL TIP

RADIATION DOSE SETTING: SINGLE LOT VS. FULL VALIDATION OF MINIMUM STERILIZATION DOSE

When establishing a dose for radiation processing, manufacturers can perform either a single lot validation or a full validation. This TechTip will explain the differences between the two validation options and outline the advantages and disadvantages of each of these approaches to dose setting.

The current standards/guidance documents most often cited for radiation sterilization are ISO 11137 and ISO TIR 13004. These standards and related guidance documents give recommendations and requirements for products to be sterilized with irradiation processes that need to make and maintain a sterility assurance level (SAL) claim for either a single lot of product, or for product that is produced routinely and has completed a full validation.

When a radiation technology, such as gamma, electron beam, or X-ray, is selected for product sterilization, the dose at which the product is irradiated must be established and validated in accordance with the appropriate standards.

The methods below outline the dose setting and substantiation methods available, based on bioburden quantity (in colony forming units/CFUs) and resistance of the organisms (D values):

BIOBURDEN-BASED DOSE SETTING METHODS

Method	Standard	CFU maximum permitted Limits
Method 1	ISO 11137-2 Table 5 and 6	1,000,000
VDmax 15	ISO 11137-2 Table 10	1.5
VDmax 17.5	ISO TIR 13004 Table 5	9
VDmax 20	ISO TIR 13004 Table 6	45
VDmax 22.5	ISO TIR 13004 Table 7	220
VDmax 25	ISO 11137-2 Table 9	1,000
VDmax 27.5	ISO TIR 13004 Table 8	5,000
VDmax 30	ISO TIR 13004 Table 9	23,000
VDmax 32.5	ISO TIR 13004 Table 10	100,000
VDmax 35	ISO TIR 13004 Table 11	440,000

Note: Method 2, is also found in ISO 11137-2, is also an available option for setting a sterilization dose. It is not a bioburden test-based method and is used less frequently so the details of it are not included in this TechTip.

FOR MORE INFORMATION

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Full Dose Validation

Full Dose Validation Steps:

1. Bioburden is tested from **three** different production lots of product to show process control in accordance with ISO 11737-1.
2. Bioburden recovery efficiency is performed to validate the bioburden test method.
3. Bacteriostasis/Fungistasis testing is performed to validate the sterility test method.
4. Consult ISO 11137-2 or ISO 13004 dose tables, as appropriate, to obtain the appropriate verification dose.
5. Tests of Sterility are performed in accordance with ISO 11737-2 using test samples irradiated at the verification dose.

Time Considerations for Full Dose Validations:

- Microbiology tests have required incubation times in order to be valid, as listed in the applicable standards (ISO 11737-1 and 11737-2) and associated laboratory standard operating procedures.
- Maximum allowable dose should be evaluated prior to confirming the dose setting method in order to assure a deliverable dose range is achievable with the minimum dose setting method selected. This testing is required to assure the product will still be safe, effective and meet its specifications if the selected maximum allowable dose is reached in terminal sterilization.
- Required microbiology tests cannot all be done simultaneously. Microbiology tests are considered destructive and product samples cannot be used for other tests.
- Product specifics or other factors that can affect timing:
    - Product may be difficult to work with (for example size, disassembly, antibacterial, adhesive, etc.)
    - Selection of Sample Item Portion (SIP)
    - Laboratory schedules (availability of reagents and staff specific to product needs)
    - Irradiation time (schedules, volume)
    - Product availability (necessary quantities, manufacturing time, component availability, etc.)
    - Transportation time
    - Test results (test results will depend on the validation method used; designed specific to the product needs)

Single Lot Validation

Single lot validations may be considered if one of the following conditions apply:

- Product manufacturing is infrequent and small batches are produced, which may not meet the tree-batch criteria for full validation
- If the product is not in its final design and expected to be modified

Single Lot Validation Steps:

1. Maximum dose effects are documented to assure product can tolerate dose selected and the dose setting method selected can result in a deliverable dose range.
2. Bioburden is tested from the one lot of product to be validated.
3. Bioburden recovery efficiency is performed to validate the bioburden test method.
4. Bacteriostasis/Fungistasis is performed to confirm validation of sterility test method.
5. Sterility testing is performed at the verification dose from the single lot to be validated.

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Note: Three single lot validations (three lots tested separately over time) of the same product (same materials (types and sources) and manufacture may be combined to achieve a full three lot validation. The lots after the first lot will not need to repeat of Maximum dose testing or method development (Recovery and B/F).

Time Considerations for Single Lot Validations:

Factors affecting timing for single lot validations are the same as in full lot validations listed above for the first lot tested.

If a single lot validation requires only one lot/batch for testing, why would anyone do a full validation?

- Single lot validation results apply only to the lot/batch tested, not to future lots. Full validations apply to future lots as long as the production process is in control. If future lots do not have product changes, full lot validation will be the most efficient method in terms of time and total cost. With a full validation all three lots of bioburden can be done concurrently and only one sterility test is needed to substantiate dose for lots tested in dose setting exercise and future lots.
- Total time and cost to reach full validation is higher if testing one lot at a time. If three single lots are tested and completed over time, the results of the bioburden tests can be applied to a full validation (determine verification dose based on the average of the three lots tested). Until testing of three lots are completed, and only if the product production process remains unchanged, can the test lots be combined to determine one ongoing verification dose. Overall, the single lot approach will mean more testing and samples.
- Each lot tested is not valid as sterile until its testing is completed.
- Small production lot sizes may require more than one lot to complete a study.

Notes: If the product production process changes lot-to-lot (for example sources of materials, design, location of process, things that can affect bioburden type or quantity, etc.), then the lots cannot be combined into a full validation until three lots of the same process and design are completed. They are still valid, though, as single lots if tested no matter how many lots are made and tested. Single lot validations are not limited in the number of times it can be used.

Reaching a full validation at minimum adds three times the sterility testing and irradiation testing costs for those samples to be irradiated when available. If product remains unchanged and test methods do not change, B/F and recovery do not need to be repeated for the second and third lot to reach the full validation point.

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COMPARISON			
Test Product (units tested must represent product manufacturing)	**Full Dose Validation**	**Single Lot Validation (SLV)**	**Addition Comments**
Bioburden	30 unirradiated samples, 10 from each of three different production lots	10 unirradiated samples from lot to be validated	
Bioburden Recovery Efficiency	3-5 irradiated samples for Inoculated recovery Alternative method exhaustive recovery may be used for some products using the bioburden test samples; should be discussed with testing lab to determine if appropriate	Same as full validation	In SLV, if product production process, design, and testing lab remain unchanged, recovery is not repeated for future lots
Bacteriostasis/ Fungistasis (B/F)	Minimum of 3 irradiated samples per media tested	Same as full validation	In SLV, if product production process, design, and testing lab remain unchanged, test is not repeated in future lots
Tests of Sterility	10 from a single lot irradiated at the verification dose for VD max methods, 100 for Method 1	10 per lot tested (30 total if three lots tested independently as separate single lot validations for the three lots needed to complete a full validation) For a Method 1, 100 per lot tested (300 total for three lots tested over time to complete a full validation)	Each lot in SLV may have a different verification dose Each will be irradiated prior to testing after the verification dose is determined
Maximum Dose	Number of units selected by Customer, based on testing required, to document product effectiveness, safety and assure specification required are maintained	Same as full validation	If future SLVs are of products with significant changes in material, process, etc., they may need to be re-tested for max dose

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Each approach has advantages and disadvantages relative to the product needs.

ADVANTAGES AND DISADVANTAGES		
Validation	Advantages	Disadvantages
Full Validation	Lowest cost of testing to reach ongoing terminal sterilization dose validations Least total product used to reach full validation No delay in use of a new lot produced waiting for additional test results	Needs bioburden units from three separate product lots After testing, dose determined will need to be substantiated with quarterly dose audits* If product changes significantly, validation may need to be repeated or further testing completed to support effects of changes
Single Lot Validation	Ideal for new products where there are no immediate plans for future production lots (ex. clinical trials, infrequent production, expected design or production changes are unlikely, proof of sterilization or concept, etc.) Will use fewer samples than full validation and have lower test costs if ongoing production is not needed Can spread costs over time (lab and production) by not making product until needed No dose audits (since each lot produced is validated) until full validation is achieved	Applies only to the lot tested, next lot produced will need to be tested before release If an additional lot is needed to continue or repeat a trial, there will be a delay in sterilization while testing is completed Scheduling of production for future lots will need to consider time to complete a new single lot validation

Additional Considerations

- The most important point of consideration is that the results of a single lot validation apply only to the lot tested, not future lots, even of the same product, until the full validation process is completed.
- Product that will likely change after a trial (as most will) frequently benefit from a single lot validation. This avoids making more product than needed or having product on the shelf that is no longer in the preferred design if changes are made. This would not be true if lots are very small and many are needed to complete the trial/study.

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- Dose audits do not usually require delays in product being terminally sterilized and released while testing is ongoing. The exception would be if a product concern is being evaluated.
- Dose audit requirements, when needed, are described in the standards listed above and in a separate TechTip (Comparison of AAMI Methods for Setting of Minimum Sterilization Dose with Irradiation). Timing is usually quarterly (every three months of manufacture).
- Routine bioburden monitoring should also be conducted to support product released in between dose audits.
- If three single lot validations are completed to achieve a full dose setting validation, the verification dose to use or future dose audits is determined based on the three lots tested.

Note on Method 2 Testing: Method 2 is not included in this TechTip due to less frequent use and more specialized applications. Dose is not based on bioburden quantity, but on resistance (D values), so Method 2 is operationally different than Method 1 or the VD max methods listed in this document. Tables are not used to set dose in Method 2, either.

REFERENCES

1. ISO 11137-1:2006, *Sterilization of health care products - radiation - Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices*

2. ISO 11137-2:2006, *Sterilization of health care products - radiation - Part 2: Establishing the sterilization dose*

3. ISO TIR 13004:2013, *Sterilization of health care products - radiation - Substantiation of selected sterilization dose: Method VDmaxSD*

4. ISO 11737-1:2018, *Sterilization of health care products - microbiological methods - Part 1: Determination of a population of microorganisms on products*

5. ISO 11737-2:2019, *Sterilization of health care products - microbiological methods - Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process*

6. Additional TechTips on dose setting and dose audits are available on STERIS AST website (https://www.steris-ast.com/techtips/)

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