Terminal Sterilization of Human and Veterinary Drug Products

Since 1994 the FDA has accepted and encouraged the use of terminal sterilization for Human and Veterinary Drug products. The acceptance of terminal sterilization is demonstrated in the Center for Drug Evaluation and Research (CDER), Center for Veterinary Medicine (CVM), November 1994, *Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*. In addition, the USP supports terminal sterilization and the methods for such are defined in USP <1222> *Terminally Sterilized Pharmaceutical Products—Parametric Release*.

The terminal sterilization processes may be used singly or in combination to sterilize a drug product. Radiation (gamma or electron beam) is one of the terminal sterilization methods listed and discussed in the Guidance Document. The guidance document defines the controls necessary for radiation sterilization which include:

1. The Facility and the Process

The radiation facility should be identified. The radiation source, method of exposure (i.e., movement through the irradiator), and the type and location of dosimeters used to monitor routine production loads should be described. If the low dose site is not used for routine monitoring, data that show the dose relationship between the two sites should be provided.

2. The Packaging of the Product

The packaging of the drug product within the shipping carton and within the carrier should be described.

3. Multiple-Dose Mapping Studies

Multiple-dose mapping studies for identification of low and high dose sites and demonstration of uniformity and reproducibility of the process should be described.

4. Microbiological Methods and Controls

The microbiological methods and controls used to establish, validate, and audit the efficacy of the cycle should be described.

In addition, FDA has made a commitment to industry to recognize AAMI, ISO, and ASTM standards as meeting the requirements for sterilization of healthcare products and drug products. Below is a list of the recognized AAMI/ISO standards recognized by the FDA with regard to Radiation Sterilization.

FDA Recognized Consensus Standards: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/results.cfm

Date of Entry	Specialty Task Group Area	Recognition Number	Standards Developing Organization	Standard Designation Number and Date	Title of Standard
07/15/2019	Sterility	14-528	ANSI AAMI ISO	11137-1:2006/(R)2015	Sterilization of health care products - Radiation - Part 1: Requirements for development, validation, and routine control of a sterilization process for medical devices [Including: Amendment 1 (2013) and Amendment 2 (2019)]
06/07/2018	Sterility	14-510	ANSI AAMI ISO	11137-3:2017	Sterilization of health care products - Radiation - Part 3: Guidance on dosimetric aspects of development, validation and routine control
04/04/2016	Sterility	14-409	ANSI AAMI ISO	11137-2:2013	Sterilization of health care products - Radiation - Part 2: Establishing the sterilization dose

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Terminal sterilization can prevent the risk of a non-sterile compounded pharmaceutical. The sterilization radiation dose (SAL Dose) is based upon the bioburden of the product in its final package and the desired Sterility Assurance Level (SAL) which, as defined in the ISO standards is an SAL of 10^{-6}. The SAL represents the probability of a viable organism in the representative production lot. For example, an SAL of 10^{-6} provides an assurance of no more than one (1) viable organism in 1,000,000 products.

Terminally sterilizing human and veterinary products eliminates the need for performing tests of sterility after manufacture, and therefore, product may be distributed upon completion of manufacturing, unless of course pyrogen testing is required for lot release.

The terminal sterilization process and establishment of the minimum sterilization dose is validated. Product release is based upon analysis of dosimeters that confirm sterilization dose has been achieved and the product was processed in the sterilizer in the manner specified in the sterilization specification.

The validation of sterilization is maintained by performing quarterly dose audits, maintaining bioburden in a state of control, and assessing change to product, packaging, and the manufacturing process.

The best method of establishing the minimum dose for drug products is defined in ANSI/AAMI/ISO 11137-2:2013, Sterilization of health care products - Radiation - Part 2: Establishing the sterilization dose, Method VDmax, where a sterilization dose is selected, based upon the bioburden of the product and the desired SAL. The VDmax method requires the minimum number of samples of all the methods of dose establishment, i.e., three lots 10 samples each for bioburden and an additional 10 samples for verification dose testing. After validating the sterilization dose, quarterly dose audits are performed where 20 samples from a current lot of product are selected and ten samples tested for bioburden and ten samples subjected to the verification dose to meet the established acceptance criteria.

When terminal sterilization of compound pharmaceuticals is validated in accordance with the ANSI/AAMI/ISO 11137 standard series, and subsequent quarterly dose audits are performed, performing tests of sterility to provide evidence of the SAL is no longer a valid means of release and is not permitted.