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USP 797 published new proposed guidelines for comment. Many of the new standards change/affect how 503a's make sterile compounds (this doesn't apply to 503b outsourcing facilities). Medizap / SteriTek have read the USP 797 guidelines to develop a position. The goal is to share this position with you. There is an opportunity to share this position at A4M Conference with compounders as you represent the industry affected by USP. Medizap / SteriTek plans to formally reply to USP from a private sector/industry trade perspective.

By being thought leaders, we hope to influence USP 797 guidelines while also building the advocacy and trust of the 503a compounding industry.

We want to discuss the core of the proposed regulatory changes in a position paper draft. We will then take thoughts/comments and build them into a complete and formal USP submission.

Medizap / SteriTek are uniquely positioned to bring a scientific perspective to the newly proposed guidelines and ensure understanding and use of ISO guidelines for all irradiation validation and ongoing testing since USP 797 omits detailed irradiation guidelines; therefore, we believe defaults to ISO regulatory guidelines.

Background on Terminal Sterilization via Irradiation:

Terminal Sterilization via Irradiation is regulated by ISO 11137-1.

Since 1994 the FDA has accepted and encouraged 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.

When terminal sterilization of compound pharmaceuticals is validated per the ANSI/AAMI/ISO 11137 standard series, subsequent quarterly dose audits are performed, performing sterility tests (USP 71) to provide evidence that the SAL is no longer a valid means of release and is not permitted.

The FDA has committed to the industry to recognize AAMI, ISO, and ASTM standards to meet the requirements for sterilization of healthcare products and drug products. Below is a list of the recognized AAMI/ISO standards recognized by the FDA concerning Irradiation Sterilization.

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 ofa sterilization process for medical devices

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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

Moreover, it's important to note that ISO separates terminal sterilization into three separate and distinct guidelines: Heat Sterilization, ETO, and Irradiation.

Our Industry Position:

USP bundles Terminal Sterilization as a group to include Steam Heat, Dry Heat, and Irradiation. We argue that grouping all three sterilization modalities ignores and does not recognize the advantages and disadvantages of each technology and cannot scientifically be rationalized because the Sterility Assurance Level or SAL achieved by Steam Heat / Dry Heat is 10^{-4} vs. SAL achievable by Irradiation is 10^{-6}.

Even though all three forms sterilize a drug product in their final primary packaging, Steam and Dry Heat terminal sterilization process validations are proven through biological indicators. They are discussed in USP 797, and if sterility testing is done with USP 71, it is on a sample set of CSP production lots no greater than 250 units.

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Terminal Sterilization via Irradiation is proven and documented under ISO 11137 / ISO11737. Proof of sterilization under ISO requires a full sterilization process validation to be performed and continued sterilization process validation with Dose Audits for sterility and bio-burden testing. There is no production size cap per lot on sterile units.

Only Irradiation terminal sterilization has proven SAL and validated testing methodology that would allow for a BUD set by Stability Testing. Terminal sterilization by Dry/Steam heat has a higher probability of affecting the potency of a drug; in addition, the equipment validation and ongoing maintenance allow for more margin of error in delivering the safest drug product. Dry/Steam heat terminal sterilization must comply with USP 71 and test product that has received a full sterilization dose. In comparison, Irradiation must follow ISO11137 and requires validation and ongoing testing on a product that has received a sub-lethal or verification dose for sterilization and still prove sterile.

Therefore, overall, our position is that if terminal sterilization by Irradiation is selected, then USP 71 does not apply. If USP 71 does not apply, the newly proposed USP 797 limit of 250 units per lot does not apply. We also propose that if Category 3 requires Stability Testing under a proven scientific method, extension or reduction of the CSP BUD be allowed and used instead of a standard table.