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USP <797> Pharmaceutical Compounding – Sterile Preparations has historically discussed in detail two main types of sterilization: aseptic processing and terminal sterilization. Though the delineation between these methods has long been discussed in iterations of the guideline, new USP <797> guideline changes that went into effect November 2023 make beyond use dating (BUD) partially contingent on sterilization method. Per guideline updates, compounded sterile preparations (CSPs) that have undergone terminal sterilization as opposed to only aseptic processing may generally receive a longer BUD, all other things being equal. Considering that, this blog post aims to review aseptic processing and various terminal sterilization methods and offer considerations for compounders trying to determine which method will be most suitable for a given CSP.

Defining Aseptic Processing and Terminal Sterilization

Aseptic processing is defined by USP as

> A method by which separate, sterile components (e.g., drugs, containers, or closures) are brought together under conditions that maintain their sterility. The components can either be purchased as sterile or, when starting with nonsterile components, can be separately sterilized prior to combining (e.g., by membrane filtration or by autoclave)

In the context of sterilization and BUD tables provided by current USP <797> it refers to sterilization by filtration or the combination of existing sterile products in a sterile environment with no terminal sterilization step. Terminal sterilization is defined as

> The application of a lethal process (e.g., steam, dry heat, irradiation) to sealed containers for the purpose of achieving a predetermined PNSU of greater than 10−6 or a probability of less than one in one million of a nonsterile unit.

Terminal sterilization allows for an extended BUD in the context of category 2 and category 3 compounding pharmacies and the guideline notes that it is the preferred means of sterilization unless a preparation is unable to tolerate this method without degradation.

Types of Terminal Sterilization

Common types of terminal sterilization include sterilization by steam heat, dry heat, and irradiation. Steam heat, commonly referred to as autoclave sterilization, uses saturated steam under pressure to sterilize aqueous CSPs. Various time, temperature, and pressure combinations may be used if verified to be effective for sterilization, though commonly a temperature of 121˚C at 15psi for a duration of time ranging between 20-60 minutes is used.1,2 Preparations sterilized via autoclave must contain water or allow for outside saturated steam to penetrate and reach all sites for appropriate sterilization.3 This moist heat kills by irreversible coagulation and denaturation of enzymes and structure proteins, making steam sterilization rapidly microbicidal and sporicidal.4 Sealed containers to be sterilized by autoclave must contain water in order to generate the appropriate steam for sterilization. For anhydrous dosage forms for which steam sterilization cannot be used, dry heat may be considered for sterilization. Given the lack of steam, sterilization by dry heat requires higher temperatures and longer exposure times to this elevated temperature. Dry heat sterilization is primarily recommended for materials that would either be damaged by most heat or are impenetrable to moist heat.5 Dry heat has a slower rate of heat penetration resulting in a longer time to microbicidal and sporicidal effect making it not preferred unless moist heat sterilization is not an option.5 Various time and temperature combinations may be used if verified to be effective for dry heat sterilization of a given CSP, though, dry heat sterilization is usually performed at 160˚C or higher. Lower temperatures, if used, must be shown to be effective for sterilization per USP <1229.8> Validation of Dry Heat Sterilization. The CDC notes common time/temperature relationships as 170˚C for 60 minutes, 160˚C for 120 minutes, or 150˚C for 150 minutes and USP <1229.8> offers an equation for calculation of necessary duration for expected microbicidal activity at various temperatures.5,6 The use of sterilization by irradiation is less common as it is not as easily accessible to compounders and generally must be outsourced to specialized facilities. Radiation sterilization uses gamma, x-ray, or e-beams to sterilize medical devices or CSPs.7 Radiation sterilization is a less common terminal sterilization method than moist heat or dry heat, however, it may be considered for heat sensitive active pharmaceutical ingredients (APIs) or dosage forms that may not be suitable for moist or dry heat sterilization, such as some types of pellets. The dose of radiation is typically measured in kilogray (kGy) or megarads (Mrad) for this method of sterilization.8 Overall needed radiation dose can depend on several factors, though, most commonly sources cite a 25kGy (2.5Mrad) dose for sterilization of pharmaceuticals.9,10

Considerations for terminal sterilization

To determine if a specific CSP is a candidate for moist heat or dry heat terminal sterilization methods we must consider the below:

1. Does the preparation contain water?
2. Is the preparation, including API and any relevant excipients such as preservatives, known to be stable to dry or moist heat?
3. Is the preparation able to be sterilized in the final container closure?

With regards to container closure, it must be stable to temperatures above those used for moist and dry heat sterilization and not a risk for leaching or deformation at higher temperatures. For example, low- and high-density polyethylene containers, while they may be considered for chemical or radiation sterilization, have poor stability to autoclave and dry heat sterilization given their low melting temperatures. Alternatively, some polypropylene based containers, while not a good option for dry heat sterilization, may be considered for autoclave sterilization.11 In addition to individual APIs, excipients, and container closure considerations, it should be noted that factors such as interaction between APIs or APIs and excipients or chemical characteristics of the preparation such as pH can also influence thermal stability of a preparation.

Summary

USP <797> guidelines have placed an emphasis on terminal sterilization methods as the preferred sterilization option over aseptic processing. Additionally, CSPs that undergo terminal sterilization may receive longer BUDs than those subjected to aseptic processing only, incentivizing pharmacies to pursue terminal sterilization in order to provide patients with a more convenient option that may require fewer visits to the pharmacy. To help pharmacies evaluate their preparation as a candidate for terminal sterilization using heat methods, we prepared resource documents for our FACTS members: Thermal Stability of Various APIs and Preservative Comparison Chart.

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