MediZap
Advanced Sterilization

Guidance on Ophthalmic Sterile Drug Compounding Enhanced by Terminal Sterilization by Irradiation

When an FDA-approved sterile ophthalmic drug from a licensed manufacturer is unavailable, pharmacists are asked to prepare sterile drug products intended for ophthalmic administration. Additionally, ophthalmologists have articulated the opportunity for compounders to combine multiple drug prescriptions into a combined commercially compounded product. In both instances, the medical practitioner sites opportunity for increased patient compliance and procedural outcome. Sometimes these sterile drug products are administered topically, in solutions, suspensions, or ointments, and other times they are administered through subconjunctival or intraocular (e.g. intravitreal and intracameral) injection.

The most crucial factor in either situation is the sterility assurance level of the drug products. Secondarily, the accuracy in measuring and preparing doses ensures the potency of active ingredients. Microbial contamination can cause an ocular infection and potential vision loss, which can be avoided through a validated terminally sterilized methodology. While dry heat or steam heat terminal sterilization improves upon an aseptic filtration methodology, there are potential deleterious effects with the potency of the compounded drug preparation. Moreover, terminal sterilization through irradiation (E-Beam | X-Ray) offers the highest Sterility Assurance Level (SAL) and the least potential degradation of API potency. Preparation and technique are the two common error factors when dealing with intravitreal solutions, which can dramatically affect the dosage and administration. To ensure success, terminal sterilization by irradiation of drug products can help increase the overall quality, safety, and performance of the treatment regiment.

The following guidelines are intended to support the pharmacist in preparing compounded ophthalmic drug products. These recommendations help ensure the quality of overall administration, dosage, potency, and usage of ophthalmic drug products. These guidelines apply to the compounding of sterile drug preparations as defined in state and federal laws and regulations.

1. Always ensure that the APIs and excipients you use have been approved for eye administration. If there is no documentation to help support this practice, you must use your own judgment before compounding the ophthalmic drug commercial product.

2. The crucial factors to consider before compounding any ophthalmic medication include the following:

a. Sterility
b. Tonicity
c. pH, buffering
d. Inherent toxicity of the drug
e. Need for a preservative
f. Solubility
g. Stability in an appropriate vehicle
h. Viscosity
i. Packaging and storage of the finished product

3. An SOP must be written for each compounded ophthalmic drug product and kept on file. Always be sure to outline specific sterilization methodologies and sterilization process validations.

4. Regardless of the size of the dose or its potency level, always have somebody else (e.g. Quality Representative) double-check your math. Intraocular injections require the most caution. They have the least dosage, which often require multiple dilutions and therefore they have a higher error level.

5. Using larger volumes in compounding ophthalmic products is best and will decrease the number of errors in measurement caused by the equipment itself. However, using larger volumes, especially in ointments, requires a higher level of attention and more usage of the API's and excipients.

6. Terminal sterilization is the last step in the compounding process for many parenteral drug products meant to be sterile for commercial distribution. The more sensitive the drugs and their primary packaging materials are, the more critical this process is. While terminal sterilization by heat (dry, steam) is required over an aseptic technique, due to significant heat exposure (temperature, duration), there is potential for deleterious effects on the potency of the compounded drug finish product. By choosing terminal sterilization via irradiation (E-Beam, X-Ray), you minimize potential post sterilization potency shortfalls. With the selection of a terminal sterilization methodology, you are delivering the highest sterility assurance and can avoid all of Guideline 7 and its subsections as it pertains to aseptic sterilization by filtration process.

7. Although the aseptic technique of sterilization by filtration is sub-optimal and sub-par regarding delivering the safest and most effective sterile drug product, if you can prove that terminal sterilization methodologies are not feasible based on raw materials and primary packaging, an aseptic technique is your only option. Compounding of ophthalmic products should be performed in a certified laminar airflow hood (or, for preparing cytotoxic or hazardous agents, a biological safety cabinet). Only personnel trained and proficient in the techniques and procedures should prepare ophthalmic products. Quality-assurance principles for compounding sterile products aseptically should be followed, and methods should be established to validate all procedures and processes related to sterile product preparation. In addition, the following should be considered:

a. Ingredients must be mixed in a sterile empty container large enough to hold the mix sufficiently. Separate syringes can draw individual components and then be injected into the needle-free tip of the larger syringe.

b. For best measurement, we recommend using the smallest syringe you can use for volume. Using two separate syringe loads is appropriate when the approximate volume requires two measurements (e.g. measuring 4.5 mL in a 5-mL syringe with no mark at the 4.5-mL level).

c. Use a sterile, disposable needle and syringe for each step to avoid errors and prevent contamination of residual contents.

d. Always label the containers of interim concentrations to avoid confusion.

e. When preparing an ophthalmic product from either (1) a liquid from a glass ampul or (2) a reconstituted sterile powder, you must filter any particulate matter through a .5-um filter to ensure success.

8. When sterile ophthalmic preparations are needed, the validation must be established in accordance with the compounded drug product formularies and primary packaging. Today's most common method to achieve sterility aseptically is through filtration of 0.22-um inside the ready to use (washed, depyrogenated, sterile) primary packaging final container, except for sterilizing ophthalmic suspensions and ointments. When an ophthalmic preparation is compounded, it can be sterilized in its final container via terminal sterilization before being dispensed. Please be advised that sterilization is always recommended in its final packaging to best achieve overall product quality.

9. Preservative-free ingredients should be used in the preparation of intraocular injections since some preservatives are known to be toxic to many of the internal structures of the eye.

10. The pharmacist should adhere to established safety guidelines when preparing ophthalmic products from cytotoxic or other hazardous raw materials.

11. To achieve the highest level of efficacy and stability of the ophthalmic product and ensure the highest administration quality, terminal sterilization is always recommended in final packaging. This is the standard recommendation when dealing with most ophthalmic solutions, including ophthalmic droppers, vials, and pre-filled syringes. Ophthalmic ointments should also be sterilized inside ophthalmic packaging tubes. All containers should be adequately sealed (container closure testing) to prevent contamination.

12. Assigning appropriate expiration dates for extemporaneously prepared ophthalmic products is essential for ensuring patient safety and efficacy of the product. Stability data, including chemical and microbial stability, should be considered in determining the product's shelf-life. The pharmacist should also consider the compatibility of the packaging material with the product and the potential for leaching of harmful chemicals into the product over time (leachable and extractable testing). Appropriate labeling of the sterile drug product with the expiration date is also essential for ensuring that medical doctors and patients do not use expired products.

13. In addition to the above, labels should also include any specific instructions for use, such as dosage and administration frequency, and any potential side effects or warnings. Clear and legible labeling is essential to ensure patient safety and proper medication use. If the ophthalmic product contains multiple ingredients, the label should clearly list all ingredients and their respective quantities or concentrations. Finally, it is important to ensure the label is securely affixed to the packaging and cannot be easily removed or damaged during transport or storage.

MediZap can provide Steri-Packs, secondary packaging used to terminally sterilize all ophthalmic solutions for our customers through our E-Beam | X-Ray irradiation machines.