College Pharmacy
Compounding Specialists

May 13, 2021

Texas State Board of Pharmacy
333 Guadalupe St #3
Austin, TX 7870-1333

Dear Board Members,

Guidance Request for (Rule 291.133(d)(2)(D)(i)(l) as this applies to the hormone pellet compounding process at College Pharmacy (non-sterile process) and the terminal sterilization process (ebeam sterilization) by an outside 3rd party provider.

In order to consider the above guidance request , it is important that every board member understand the pellet compounding process, and the difference between this process and the compounding of sterile, injectables and ophthalmic preparations., compounded by aseptically filtering a preparation into a sterile vial or ophthalmic container.

Non-Sterile Process at Pharmacy

Although this process is a non-sterile process, every attempt is made to minimize bioburden. This is done by proper use of PPE (hair & shoe covers, gloves, masks, & gowns) and proper cleaning of all surfaces, hoods, and pellet presses..
Under pharmacist supervision, technicians weigh non-sterile powders, and press various strengths of solid pellets. The pellets are visualized & cleaned, and then put into non-sterile tubes with screw tops, and then labeled.
No aseptic technique is used. No filtering is used. The final preparation compounded at the pharmacy is a non-sterile pellet in a non-sterile tube.

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Terminal Sterilization by Steritek, an FDA registered, ISO 11137 certified provider of ebeam services (cGMP Process Validated

1.. Pellets are cleaned (powder dust removed), visualized (defective pellets discarded), and then inserted into an approved & tested non-sterile screw top tube. This is done in an ISO 5 Biological Safety Cabinet in a negative pressure, ISO 7 clean room, per USP 800.

2. Pellet tubes (non sterile) are labeled and then put into Ziploc bags (288 tubes per bag).

3. A maximum number of bags are put into a cardboard box and shipped by FedEx to a FDA registered E-Beam facility in California for processing.

4.The pellets are processed by an e-beam facility after extensive dose audits are performed to determine precise dose required to kill all organisms, and quarterly dose audits and bioburden studies are done to ensure that process is effective.

5. Sterile pellets are shipped to College Pharmacy with an official E-Beam Certificate. This process conforms to ISO 11137, the FDA approved standard which manufacturers must follow.
As an added precaution, not required by ISO 11137, College Pharmacy sends a representative sample of the e-beamed pellets to a third party lab for USP 71 sterility testing.
College Pharmacy has never had a pellet sterility failure. The sterilization of our pellets has been process validated, and complies with a higher standard than aseptically filtering solutions per USP 797.

The sterility assurance level (SAL) describes the probability that a viable colony forming unit (CFU) survives sterilization. The SAL for terminal sterilization by ebeam radiation is 10-6 (1 in 1,000,000 chance of survival).

Compounding of Injectables Using Aseptic Technique

1. Sterilization is accomplished by filtering the preparation into sterile glass vials, using a 0.2 micron filter. Personnel must maintain good aseptic technique during all phases of the compounding process to ensure sterility of the final preparation.

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2. Proper cleaning and garbing is required to reduce bioburden.

3. The final preparation compounded in the pharmacy must pass the sterility, fungal & endotoxin test and be quarantined until results are obtained. The SAL (sterility assurance level) for aseptically processed preparations, is 10-3 (1 in 1000 chance of survival). Terminal sterilization by ebeam radiation is 1000 times more effective than sterilization by filtering using aseptic technique.

4. Media-fill or process simulation test should mimic an actual and entire compounding procedure, using a suitable growth medium, such as tryptic soy broth (TSB), in place of the typical ingredients, to prepare a finished compounded preparation. This process verifies an employee's aseptic technique, and is only necessary for preparations which are filtered, not terminally sterilized. Since there is no aseptic filtering and no aseptic technique used in the pellet department, and the final preparation compounded in the pharmacy is non-sterile, it is obvious that the pellet compounding process is a completely different process than compounding sterile injectables. Therefore, the training of all staff involved in compounding should reflect the specific process being followed on a daily basis. Media fills, gloved-fingertip testing and aseptic technique are necessary when compounding injectables, not pellets.

Therefore, I am requesting that the board seriously look at all the facts, and not require aseptic training and certification for staff not involved in aseptic compounding. As far as patient safety, our process validated pellet process is 1000 times more effective than our aseptic filtering of injectables.

Sincerely,

Jerry Gillick, RPh
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Texas P.I.C.

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WHO good manufacturing practices for sterile pharmaceutical products

1. General considerations

1.1 The production of sterile preparations should be carried out in clean areas, entry to which should be through airlocks for personnel and/or for equipment and materials. Clean areas should be maintained to an appropriate standard of cleanliness and supplied with air that has passed through filters of the required efficiency.

1.2 The various operations of component preparation (such as those involving containers and closures), product preparation, filling and sterilization should be carried out in separate areas within the clean area. These areas are classified into four grades (see section 4).

1.3 Manufacturing operations are divided here into two categories:

— first, those where the product is terminally sterilized; and
— second, those which are conducted aseptically at some or all stages.

2. Quality control

2.1 The sterility test applied to the finished product should only be regarded as the last in a series of control measures by which sterility is assured. The test should be validated for the product(s) concerned.

2.2 Samples taken for sterility testing should be representative of the whole of the batch but should, in particular, include samples taken from parts of the batch considered to be most at risk of contamination, for example:

- for products that have been filled aseptically, samples should include containers filled at the beginning and end of the batch and after any significant interruption of work;
- for products that have been heat sterilized in their final containers, consideration should be given to taking samples from that part of the load that is potentially the coolest.

2.3 The sterility of the finished product is assured by validation of the sterilization cycle in the case of terminally sterilized products, and by "media simulation" or "media fill" runs for aseptically processed products. Batch-processing records and, in the case of aseptic processing, environmental quality records, should be examined in conjunction with the results of the sterility tests. The sterility test procedure should be validated for a given product. Pharmacopoeial methods should be used for the validation and performance of the sterility test. In those cases where parametric release has been authorized in place of sterility testing special attention should be paid to the validation and the monitoring of the entire manufacturing process.

The purpose of sterilization is to provide to the patient an efficient drug product that can be used with the highest safety level. Terminal sterilization and aseptic processing are two approaches to obtain a sterile drug product; however, they are two fundamentally different methods. For personnel within the pharmaceutical and medical device industries, this Industry Insight compares terminal sterilization and aseptic processing.

While terminal sterilization and aseptic processing are two different methods to obtain a sterile drug product, regulatory bodies in the United States (US) and European Union (EU) agree that terminal sterilization is preferred and should be considered first to minimize the risk of contamination and its consequences.

> "Wherever possible, a process in which the product is sterilized in its final container (terminal sterilization) is chosen."
>
> **— European Pharmacopoeia**

Terminal Sterilization

Terminal sterilization is achieved by exposure to a physical (e.g., temperature, radiation) or chemical sterilizing agent (e.g., Vaporized Hydrogen Peroxide (VHP), Vaporized Peracetic Acid (VPA), Ethylene Oxide (EO)) for a predetermined extent of treatment. The product is sterilized in its final packaging (or final assembled form), which highly reduces subsequent sterility risk. The process is validated to provide a Sterility Assurance Level (SAL) lower than 10-6, which means a probability of less than one unsterile product on a one million population. Terminal sterilization provides a SAL that is possible to calculate, validate and control, and thus incorporates a safety margin.

Aseptic Processing

Aseptic processing is a process performed maintaining the sterility of a material that is assembled from components, each of which has been previously sterilized. This is achieved by using adequate conditions and facilities designed to prevent microbial contamination. Aseptic processing relies on several independent factors for prevention of recontamination of previously sterilized components. Therefore, a SAL is not applicable as accidental contamination caused by inadequate technique cannot be reliably eliminated. Aseptic processing presents a higher risk of microbial contamination of the product than terminal sterilization. Any manual or mechanical manipulation of the sterilized drug, containers, or closures prior to or during aseptic filling and assembly poses the risk of microbial contamination.

Decision Making

The selection of the sterilization method follows a clearly defined decision tree that starts with terminal sterilization. There are various terminal sterilization technologies. Heat sterilization is the preferred technology. In case of temperature-sensitive products, the application of an alternative technology, ionizing radiation (Gamma or E-beam) is an alternative, followed by gas sterilization (e.g., Peracetic Acid (PA), Nitrogen Dioxide (NO2), EO). Aseptic processing is the last possibility as stated in all major standards (European Medicines Agency (EMA), US Food and Drug Administration (FDA)).

The justification for the chosen sterilization or aseptic process should include an extensive and science-based benefit risk evaluation and it should be demonstrated that suitable development efforts have been made to enable terminal sterilization (i.e., adapt formulation, container and more).

Processing

4.21 Precautions to minimize contamination should be taken during all processing stages, including the stages before sterilization.

4.22 In general, preparations containing live microorganisms should not be made, nor should containers be filled in areas used for the processing of other pharmaceutical products. However, if the manufacturer can demonstrate and validate effective containment and decontamination of the live microorganisms, the use of multiproduct facilities may be justifiable. Vaccines consisting of dead organisms or of bacterial extracts may be dispensed into containers in the same premises as other sterile pharmaceutical products, provided that the inactivation procedure has been properly validated.

When multiproduct facilities are used to manufacture sterile preparations containing live microorganisms and other sterile pharmaceutical products, the manufacturer should demonstrate and validate the effective decontamination of the live microorganisms, in addition to precautions taken to minimize contamination.

4.23 Validation of aseptic processing should include a process simulation test using a nutrient medium (media fill). Selection of the nutrient medium should be made based on dosage form of the product and selectivity, clarity, concentration and suitability for sterilization of the nutrient medium.

4.24 The process simulation test should imitate as closely as possible the routine aseptic manufacturing steps except where the activity may lead to any potential microbial contamination.

4.25 Process simulation tests should be performed as part of validation by running three consecutive satisfactory simulation tests. These tests should be repeated at defined intervals and after any significant modification to the heating, ventilation and air-conditioning (HVAC) system, equipment or process. Process simulation tests should incorporate activities and interventions known to occur during normal production as well as the worst-case situation. The process simulation tests should be representative of each shift and shift changeover to address any time-related and operational features.

4.26 The number of containers used for media fills should be sufficient to enable a valid evaluation. For small batches the number of containers for media fills should at least equal the size of the product batch. The target should be zero growth and the following should apply:

- when filling fewer than 5000 units, no contaminated units should be detected.
- when filling 5000–10 000 units:
  — one contaminated unit should result in an investigation, including consideration of a repeat media fill;