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TERMINAL STERILIZATION OF PHARMACEUTICAL PRODUCTS

In the human health field, injectable medications, ophthalmic preparations, irrigation fluids, dialysis solutions, sutures and ligatures, implants, and certain surgical dressings, as well as the instruments necessary for their use or administration, must be presented in a sterile condition. USP<797> states that:

“ Medications that are required to be sterile include those administered through injection, intravenous infusion (IV), intraocular (injection in the eye) or intrathecal (injection in the spine). ”

There is growing demand for sterilization of small-molecule parenteral products, including heart medications, eye drops, analgesics, and antibiotics, as well as common intravenous solutions such as glucose, potassium, and saline. Many such products are used by medical professionals in hospitals, and to ensure patient safety, the drug products and related instruments and materials are sterilized at manufacture. This ensures there are no microbial contaminants like fungi or bacteria present when the product is used.

TERMINAL VS. ASEPTIC STERILIZATION OF PHARMACEUTICAL PRODUCTS

Terminal Sterilization

Generally, regulatory agencies such as the FDA, EMA and others prefer terminal sterilization over aseptic, as it provides a high level of sterility assurance¹.

“ There are basic differences between the production of sterile drug products using aseptic processing and production using terminal sterilization. Terminal sterilization should be utilized when the product and container/closure system are able to withstand the terminal sterilization process. ”

With terminal sterilization, most drug products are produced by mixing the ingredients to form the bulk drug product solution. The bulk product is filled into a tightly sealed container and the entire container is sterilized.

Terminal sterilization also offers time savings and cost advantages to pharmaceutical companies. Since terminal sterilization takes place after the formulation and filling steps, these initial manufacturing processes can occur in a less rigidly structured environment, which lowers the complexity, increases the speed, and therefore positively impacts the cost of manufacturing.

The sterility assurance level (SAL) describes the probability that a viable unit or colony forming unit (CFU) survives sterilization. If a product is terminally sterilized it has a SAL of 10^{-6} (i.e., only one in one million CFUs will survive terminal sterilization), while an aseptically processed product has a higher risk SAL of 10^{-3} (a one in one thousand chance of survival).

Aseptic Processing

When terminal sterilization is not an option, aseptic processing is used. Each component (drug, container, closure, etc.) is individually sterilized first, then carefully assembled in a dedicated clean room with a highly controlled environment to make the finished drug product in a manner that prevents contamination. Containers, closures, and filling materials go through their own validated sterilization cycles.

Aseptic processing cannot provide the same quantitative level of sterility assurance as terminal sterilization, but it features several layers of control to minimize the risk of contamination.

In sterile filtration, the final drug product solution is passed through a filter that has itself been terminally sterilized and designed with appropriate pore sizes/surface chemistries to remove bacteria via size exclusion, entrapment, electrostatic attraction, and other modalities. The filtration step of the formulated drug product manufacturing process must be validated by demonstrating repeatedly that passing the product through the selected filter removes microorganisms below a defined level. For this validation, a bacterium of very small size (even compared to other bacteria), which is therefore more likely to pass through a filter, is used.



The clean room environment where the filling takes place is strictly controlled. Operator gowning in an aseptic processing area typically requires full coverage – no exposed hair or skin – with sterile coveralls, hoods, boots, goggles, and gloves. Operators are highly trained in all techniques, and each operator must pass certification testing before they can participate in aseptic activities.

The entire aseptic process is routinely simulated in a challenge that is designed to detect the potential for contamination in the finished drug product. A single unit positive for growth is a sign that the process has failed and needs to be thoroughly investigated – zero positives is the norm for this challenge.

There are several variations on aseptic processing. In addition to the traditional clean room, some facilities use barriers to separate operator from the actual filling area. These can be full isolators completely closed to the surrounding environment, or less enclosed systems such as RABS (remote access barrier systems). Both require operators to interact with the filling area only through special glove ports, further minimizing the potential for contamination of the drug product.



TERMINAL STERILIZATION METHODS FOR PHARMACEUTICALS

Radiation exposure is a highly effective sterilization method used for pharmaceuticals and medical products. Radiation destroys the DNA of the contaminating microorganisms, inactivating them and producing a completely sterile product. Even closed packages are reliably sterilized by beta and gamma rays.

Although beta and gamma radiation are the most used, there are other options such as infrared and ultraviolet radiation, and high-velocity electrons. Radiation is typically used for the sterilization of packaged drug products and single-use components/systems.

Both beta and gamma rays are suitable for sterilization. The main differences between them are depth of penetration and dose rates.

Beta rays (also called Electron Beam or E-Beam) have limited penetration depth, and a high dose rate.

In beta ray treatment, electron accelerators are used to emit an electrical field which neutralizes any bacteria or fungi and delivers a sterile product. The beam is a concentrated, highly charged stream of electrons, generated by accelerators capable of producing continuous or pulsed beams. As the product passes the E-Beam, energy from the electrons is absorbed, which alters chemical bonds, damages the DNA, and destroys the abilities of the microorganisms to reproduce. Some materials – certain polypropylenes, for example – are less likely to break down and are spared long-term aging effects because of beta rays' shorter exposure time as compared to gamma rays.

Electron accelerators can be compared to the construction of a cathode ray tube. A hot cathode emits electrons which are accelerated in a high-vacuum, strong electrical field, up to 5 megaelectron volts (MeV). If energies greater than 5 MeV are required to ensure a sterile product, resonance accelerators are used. In these, electrons are accelerated in a cyclic alternating field in several stages, up to a maximum energy of 10 MeV. On leaving the accelerator, the electron beam is deflected into a fan shape before it reaches the products to be irradiated.



Gamma rays have a lower dose rate and high penetration capability.

During gamma irradiation, whole pallets of products are transported into a gamma plant on a conveyor belt. The gamma rays used in the plant result from the decay of the radioactive isotope Cobalt-60 (^{60}Co). The products are carried around the source rack which houses the radiation sources. The gamma rays have a high penetration depth and can penetrate complete pallets of product.

The process control system is precisely adjusted to account for each individual product on the pallet, ensuring that each pallet makes the predefined number of circuits around the plant. In this way, the total gamma irradiation dose that has been specified during validation for each product is exactly applied.

Table 1. Characteristics of Terminal Sterilization Methods.

PARAMETER	BETA RAYS (E-BEAM)	GAMMA RAYS
Dose rate	High	Low
Irradiation time	Seconds	Hours
Energy source	Electric current	Cobalt-60
Safety	Electric current interruption	Shield
Penetration depth	Low	Very high
Irradiation unit	Individual boxes	Pallets

EMPHASIS ON VALIDATION

Because sterilization is crucial in the manufacture of drug products and is key to ensuring patient safety, rigorous controls are implemented to ensure that the final product is of the highest quality. Monitoring ensures compliance with specific good manufacturing practice (GMP) requirements and sterility assurance.

Extensive testing is conducted during the development process to identify appropriate sterilization conditions for a given drug product. The amount of time that an unsterilized product can safely be kept in its package without substantially increasing microbial contamination is first determined. The time allowed between filling and sterilization depends on the nature of the solution and its susceptibility to microbial growth. Concentrated salt solutions, for example, do not offer an ideal environment for microbes to grow. On the other hand, glucose solutions have a high likelihood of microbial proliferation. The hold times must therefore be determined according to the unique conditions of the drug product in question.

Once the appropriate sterilization process is developed, it is validated.

Validation Steps

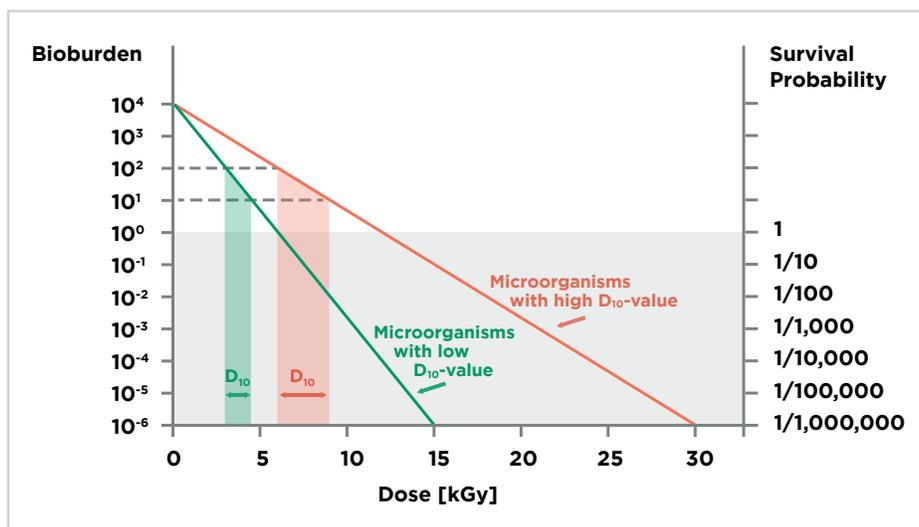
1. Microbiological validation

In microbiological validation, the radiation dose necessary to change a non-sterile product into a sterile one is determined. The initial microbiological state is assessed by determining the numbers and types of microorganisms present in an accredited microbiological laboratory. Once the bioburden and its resistance to ionizing radiation of the microorganisms is understood, experimental verification is carried out to confirm that the sterilization process delivers the required results.

Various methods of experimental verification are available – the selection depends on factors such as:

- Production conditions (degree of automation, production environment i.e. clean room production/manual production)
- Selected materials (use of natural fibres such as cotton, or synthetics)
- Batch size and production quantities, continuous production, number of products

Figure 1. Effects of Ionizing Radiation on Microorganisms.



The optimal method is selected based on an experimental assessment that determines whether the response to radiation of bioburden is greater than that of a microbial population having a standard distribution of resistance (= SDR). In this approach, the microbial contamination (bioburden) of the drug product is used as a basis for determining the sterilization dose.

To determine this bioburden, ten samples from each of three production batches are examined. The evaluation of the 30 individual tests provides an average bioburden for all the batches, and an appropriate radiation dose is determined.

A subsequent dose verification experiment is conducted, in which 100 individual samples are irradiated with the previously established dose. The actual radiation dose delivered must be within a tolerance of 10% relative to the verification dose. Post-irradiation, the 100 samples are individually tested for sterility. The verification is accepted if there are no more than two positive tests of sterility from 100 tests performed.

2. Dosimetric validation

Dosimetric validation – determining dose distribution – ensures that the minimum dose of irradiation established during microbiological validation is consistently delivered throughout the product, given the predetermined packaging specifications and packing schema. This is achieved by fixing the radiation conditions and documenting the positions of the minimum and maximum radiation doses absorbed by the packaged products.

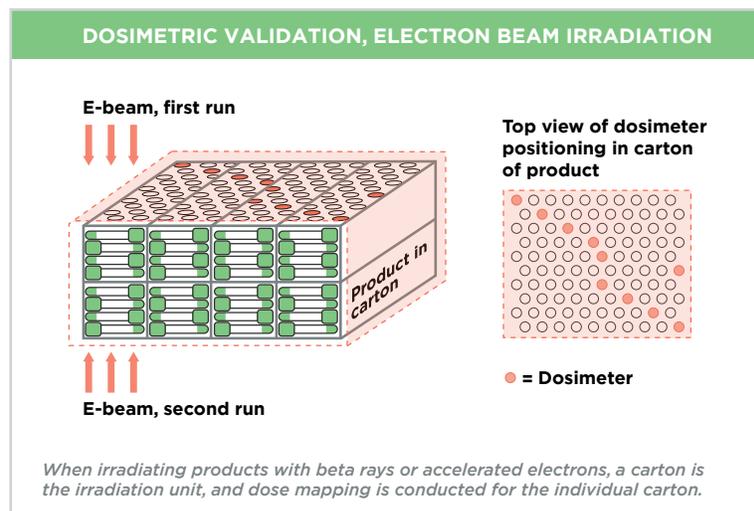
Basis:

- Specified product
- Specified packaging
- Specified arrangement of product inside the packaging
- Packing arrangement within the pallet / transport box

Determining dose distribution:

- Maximum dose positions (maxima)
- Minimum dose positions (minima)
- Positioning of the dosimeter in routine treatment to calculate the minimum and maximum dose

Figure 2. Dosimetric Validation of E-beam Irradiation.



3. Application-related validation

The dosimetric validation allows for determination of the radiation conditions and the maximum acceptable dose. Medical devices and product packaging are often partially or entirely made from plastics, or other materials that may be sensitive to radiation. It is therefore necessary to consider possible changes in the properties of these materials following the sterilization and production process.

Appropriate primary packaging serves to support and maintain the sterility of irradiated products. In application-related validation, potential changes to the medical product and its primary packaging are assessed after irradiation with the maximum acceptable dose, ensuring also that performance and properties of the product be retained for the whole lifetime declared by the manufacturer. Depending on the product, different investigations are necessary.

Table 2. Aging Assessments for Terminally Sterilized Products.

INVESTIGATION TYPE	DURATION
Accelerated aging (simulates 2 years)	5–8 weeks
Seal integrity test	2 weeks
Real-time aging	As determined

Material Changes

Irradiation destroys microorganisms, and changes material properties of packaging and devices. These changes often vary depending on the radiation dose. From the results of the dosimetric validation, the dose range within which material changes need to be tested is determined. Possible changes in material properties must be taken into account at the product development stage, particularly if plastic materials are involved.



Following radiation sterilization, application-specific tests are run to determine which polymer is optimally suited to an individual application. Products are irradiated in the appropriate dose range for the established sterility requirements.

The dose range provides an initial indication if a material is suitable for radiation sterilization. However, this overview cannot take the place of radiation testing of products within the necessary dose range.

METHOD SELECTION

Sterilization involves subjecting your product or device and its packaging to harsh conditions. Choosing an appropriate sterilization method demands a comprehensive understanding of the physicochemical properties of the drug substance, and the characteristics of the final formulated product.

For example, small-molecule APIs may be sensitive to radiation. However, in many cases, with slight adjustments to the sterilization process time, radiation can still be an appropriate terminal sterilization method.

Radiation will cause degradation of most biologic drug substances. For biopharmaceutical products, therefore, sterile filtration or manufacturing under aseptic conditions is required.

WHY TERMINAL STERILIZATION

Terminal sterilization is the preferred method for drug products because sterilization takes place after the product has been filled into the primary packaging, thus severely limiting further opportunities for contamination due to human intervention. The process is reliable, repeatable, and delivers an excellent quality product.

Terminal sterilization is also less complex, less costly, and more easily reproducible than aseptic processing. When conducted by well-trained, knowledgeable experts, sterilization conditions can be adapted to ensure they are appropriate to the drug product in question, and deliver the robust, thorough sterility results expected from this type of process.

In our Grade C suites we develop injectable drug products and topical ophthalmic preparations that can be terminally sterilized after manufacture. All such drug processing is conducted in our Grade C, cGMP facility, which has been inspected by both the FDA and the European Union Quality Personnel.

Altasciences' team of experts will guide you in the selection, method development and validation, and final delivery of fully sterilized product. We have decades of experience in the field, and will ensure the efficient, effective implementation of the most appropriate sterilization method for your drug products.

REFERENCE

1. FDA, Compliance Program Guidance Manual. <https://www.fda.gov/media/75174/download>. Accessed Nov. 29, 2021.

ALTASCIENCES' RESOURCES

Specialty Services

[Terminally Sterilized Injectables](#)

[Take a Video Tour of our Manufacturing Facility](#)

Webinar

[Advantages of Terminal Sterilization
Over Aseptic Manufacturing](#)

ADDITIONAL INDUSTRY RESOURCES

[EMA Guideline on the Sterilisation of the Medicinal Product, Active Substance, Excipient and Primary Container.](#)

[FDA Sterile Drug Products Produced by Aseptic Processing Current Good Manufacturing Practice.](#)

[FDA Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products.](#)

[FDA Guidance for Industry Submission of Documentation in Applications for Parametric Release of Human and Veterinary Drug Products Terminally Sterilized by Moist Heat Processes.](#)

ABOUT ALTASCIENCES

Altasciences is an integrated drug development solution company offering pharmaceutical and biotechnology companies a proven, flexible approach to [preclinical](#) and [clinical pharmacology](#) studies, including [formulation, manufacturing, and analytical services](#). For over 25 years, Altasciences has been partnering with sponsors to help support educated, faster, and more complete early drug development decisions. Altasciences' integrated, full-service solutions include [preclinical safety testing, clinical pharmacology and proof of concept, bioanalysis](#), program management, medical writing, biostatistics, clinical monitoring, and data management, all customizable to specific sponsor requirements. Altasciences helps sponsors get better drugs to the people who need them, faster.

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