

ASEPTIC VS. TERMINAL STERILIZATION MANUFACTURING PROCESSES FOR DENTAL ANESTHETICS IN GLASS CARTRIDGES



Introduction

Local anesthesia is the foundation of pain control in dentistry. In standard practice, the anesthetic drug product is contained in a glass cartridge, sealed at one end with a rubber plunger and capped at the other end with an aluminium cap and a rubber seal. The drug product is administered by the dentist by inserting the cartridge into a stainless steel syringe and injected into the gum of the patient.

Most dental anesthetics contain epinephrine as a vasoconstrictor and since epinephrine is readily oxidizable it requires protection by a suitable antioxidant, generally sulphite or metabisulphite.

The consolidated worldwide manufacturing process for dental anesthetics in glass cartridges is the aseptic process, although in the US the majority of dental anesthetics are manufactured by terminal heat sterilization.



Important safety information

The reason for two different processes for the same drug product is due to the effect of the heat treatment on both the components of the injectable solution (degradation and reaction between components) and on the rubber closures of the cartridges.

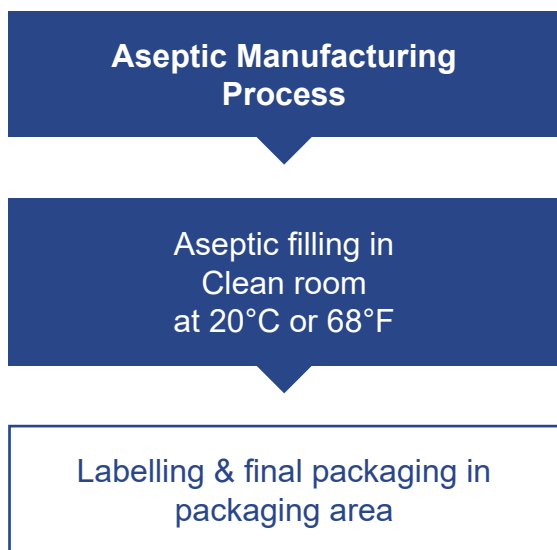
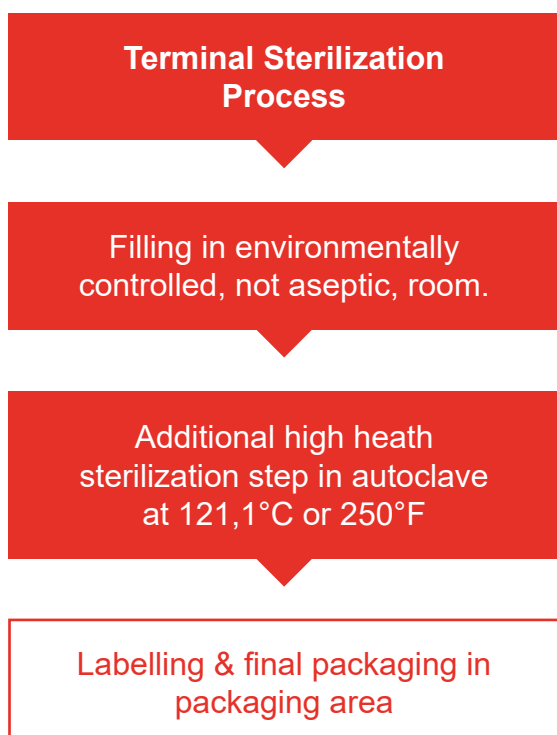
FDA and European guidelines state, “Sterile drug products should be manufactured using aseptic processing only when terminal sterilization is not feasible.” Consequently, terminal sterilization is sometimes preferred because it represents an ultimate safeguard for drug product sterility when this cannot be ensured all along the manufacturing process. However, the damaging effects of terminal sterilization on some raw materials/substances sometimes force manufacturers into aseptic processing.

In order to provide actual terms of comparisons between the two manufacturing processes, local dental anesthetics containing articaine and epinephrine marketed today in the US are considered below:

Key points of aseptic manufacturing as compared to terminal sterilization

1. Aseptic manufacturing provides less degradation of the epinephrine during the manufacturing process. **The quality characteristics are preserved during the product shelf life thus allowing articaine, when manufactured in aseptic**

- conditions, up to 24 months duration, as compared to the 18 months duration of an articaine manufactured under terminal sterilization.
2. A further consequence of point a) above, is that there is less overage of epinephrine required for the same label claim with aseptic manufacturing. The **American Heart Association recommends reducing, where possible, the use of vasoconstrictors in anesthetics.**
 3. There are significantly lower concentrations of articaine related potential impurities formed during aseptic manufacturing. **A drug product with less chemical impurities may be preferred even if the impurities do not present health issues.**
 4. Significantly lower concentrations of epinephrine related impurities are formed with aseptic manufacturing. **A drug product with less chemical impurities may be preferred even if the impurities do not present health issues.**
 5. A more stable drug product pH profile during the shelf life is produced with aseptic manufacturing. **The heat sterilization step produces a pH change of about 0.4-0.5 pH units at batch release. When manufactured aseptically, there is no change in pH. A more stable optimum pH may be essential for reproducible painless injections.**
 6. There is less degradation of the antioxidant (metabisulphite) during the drug product shelf life and improved protection of the epinephrine with aseptic manufacturing. **After 24 months at 25 °C the drug product produced aseptically still contains sufficient metabisulphite to protect the epinephrine from oxidation, while in the terminally sterilized product at the end of its shelf life (18 months) it contains almost no metabisulphite.**
 7. There is better and more constant functionality of the plunger during the drug product shelf life with aseptic manufacturing. **With aseptic production the quality of the rubber closures, especially resilience and elasticity, are more constant throughout the shelf life. In a terminal sterilization process the rubber closures are heat-treated twice (before assembly onto the cartridge and after filling), thus the rubber characteristics may vary.**
- In the terminal sterilization process, the product must be treated with a high temperature autoclave process (at least 121°C) to kill eventual microorganisms inside. The dead bacteria will stay inside the cartridge or vial.
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- In aseptic manufacturing, eventual microorganisms are stopped before the process starts and the product doesn't exceed 20°C.

**VS**

Conclusions

A terminal sterilization process should be used in cases where heat treatment has no detectable effect on the chemical entities in the solution for injection and/or the primary container rubber components. An aseptic manufacturing process should be used where heat sensitivity of the individual components of the drug is detected.

The above reasoning is supported by the fact that in the US the FDA approved articaine with epinephrine dental anesthetic produced with an aseptic process has a 24-month shelf life. The articaine with epinephrine dental anesthetic produced with a terminal sterilization process has an 18-month shelf life.

The working block diagram, is shown illustrating the core manufacturing of the two processes where the filling room makes the difference. In an aseptic manufacturing process, the filtered anesthetic solution is filled at room temperature in an aseptic zone; while in a terminal sterilization process, the cartridge is filled in a not aseptic zone and needs to be sterilized in an autoclave at high temperature to ensure aseptic conditions.

Above - Aseptic vs terminal sterilization working block diagram.

MANUFACTURING PROCESS DESCRIPTION		DIFFERENCES
Aseptic processing		Asepsis processing vs Terminal sterilization
1	Drug product, container and closures are sterilized and brought together in aseptic conditions.	Product containers are filled and sealed under high quality conditions to minimize contamination, but not to guarantee sterility, such to require heat sterilization
2	Because there is no process to sterilize the product in its final container, it is critical that the containers be filled and sealed in an extremely high quality environment.	Product in its final container is subjected to a heat sterilization process after filling.
3	Uses low bio-burden components.	Generally higher bioburden components can be used.
4	Relies on removal/separation of microorganisms.	Relies on a lethal treatment to microorganisms at the end of the process.
5	Currently ore widely used in Europe.	Method of choice.
6	Materials/stability generally unaffected.	Degradation of materials is always a concern.
7	Harder to control.	Relatively easy to validate.
8	No materials issues.	Not applicable to all materials.
9	No primary packaging. issue	Glass cartridge rubber closures present an issue.

