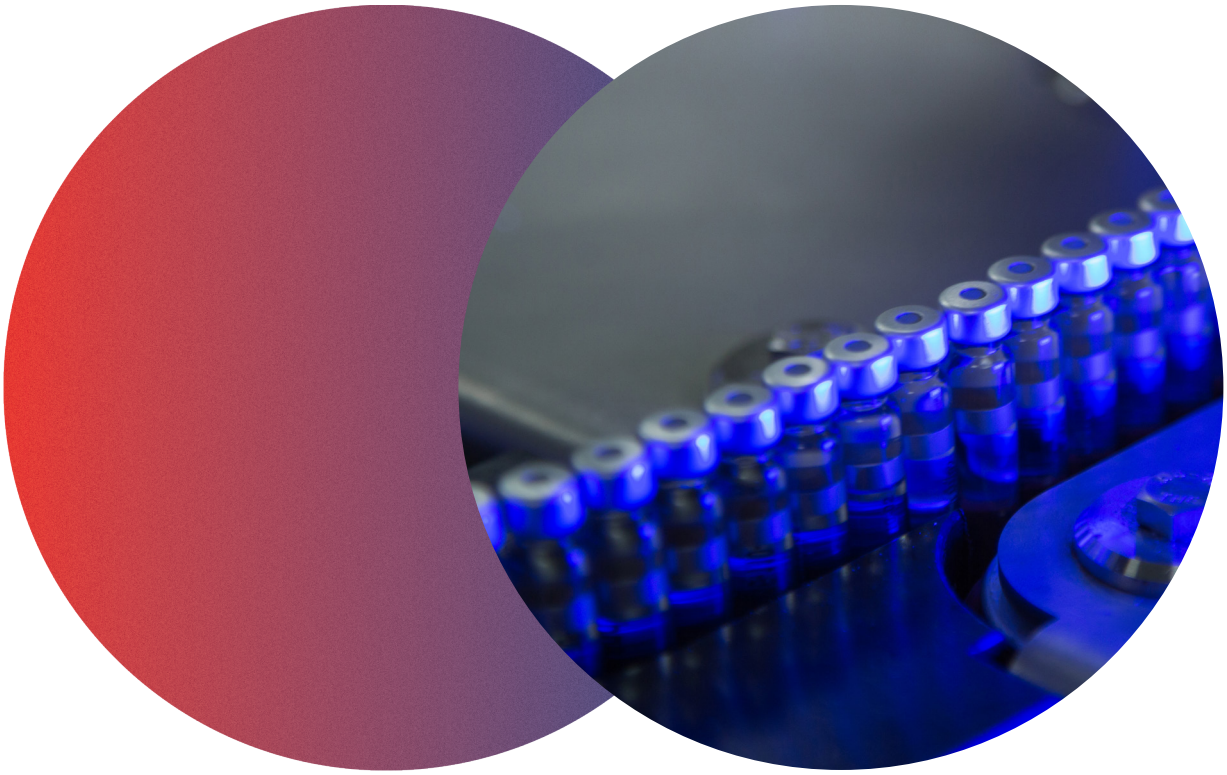
STERILIZATION IN MANUFACTURING PROCESSES FOR DENTAL ANESTHETICS INJECTABLE SOLUTION



PIERREL

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Introduction

The manufacturing process for an injectable drug product is governed by international Good Manufacturing Practices (GMP) guidelines; FDA guidance to industry and European Union GMP guidelines. Both guidelines indicate that two processed may be used, an aseptic manufacturing process or a terminal sterilization process. Although the guidelines state 'Sterile drug products should be manufactured using aseptic processing only when terminal sterilization is not feasible' **there is no law in any country which lays down that an injectable drug product should be manufactured in one way or another.**
It is up to the Market Authorization Holder to carry out appropriate scientific investigations to determine which is the most suitable process for the drug product in question and to submit the results for Health Authorities evaluation and approval.

The picture

Most dental anaesthetics contain 'epinephrine' as a vaso-constrictor and since this is readily oxidisable it requires protection by a suitable anti-oxidant, generally sulphite or metabisulphite.
The characteristics and chemistry of epinephrine are well documented in the literature[1].
The substance is rather reactive, as it a reducing substance and consequently also easily oxidized. Furthermore, the primary container closures are a rubber plunger and rubber cap seal. Consequently, the characteristics of rubber closures must also be studied during the drug product development steps in particular regarding potential extractables and leachables, and stability of the rubber characteristics at various temperatures.

The evaluation

What must be done in order to decide which manufacturing process is better for dental anesthetics containing epinephrine? This must be documented in a scientifically valid way before the drug product (DP) is approved by the Health Authorities.

For example:

Evaluate the chemical, physical and microbial characteristics and stability of all the drug product chemical entities.

Evaluate the stability and compatibility of the components of the solution for injection.

Evaluate and quantify potential extractables and leachables from the glass cartridge, rubber plunger and rubber cap seal which on contact with the solution for injection could be potentially extracted into the drug product.

Evaluate if heat treatment at say 80, 100, 120 and 130°C has any negative effects on the solution for injection, on the rubber seal and on the rubber plunger since change in hardness/ elasticity could have a negative effect on the container closure integrity and plunger sliding during drug product administration.

Execute ICH stability studies of 3 batches of DP in order to set the batch release and shelf life specifications.
After obtaining and evaluating the results of the above investigations the most suitable GMP manufacturing process can be proposed and validated.

Comparison, a practical exercise using USP compendia articaine and epinephrine injection

Summary of current USP monograph requirements of Articaine Hydrochloride 40 mg/mL and Epinephrine 1:100,000 injection:

USP Definition:
Articaine Hydrochloride and Epinephrine Injection is a sterile solution of Articaine Hydrochloride and Epinephrine in water for injection etc.

Comment:
Only general description, no mention of excipients, anti-oxidants, rubber closures and manufacturing process to be used.

Appearance:
Clear colourless solution, free from visible particles.

Comment:
This is the same for the aseptic and terminal sterilized product.

Articaine hydrochloride Assay:
38-42 mg/mL (3.8-4.2%)

Comments:
If the DP is manufactured aseptically there is no detectable change in the assay, however, if manufactured via terminal sterilization there will be a loss of 0.1-0.2% due to the hydrolysis of the articaine to form articaine acid.

Articaine related compound B (Articaine acid):
NMT 0.5% with respect to articaine.

Comment:
If the DP is manufactured aseptically the articaine acid concentration is not detectable but if manufactured via terminal sterilization concentrations of the order of 0.1-0.2% are detectable.

Epinephrine Assay:
9.0 to 11.5 mcg/mL

Comment:
The lower value permits 10% degradation of the label claim while the upper value allows 15% overage of the epinephrine due to its instability. No detectable change for the DP produced aseptically, however, since epinephrine is heat labile and reacts with the sulphite/bisulphite to form epinephrine sulphonic acid. About 5-6% of the epinephrine is lost during the sterilization process of the DP. The aseptically produced product only requires 5-10% overage while the terminal sterilization requires at least 15% overage of the epinephrine to compensate for degradation during the heat treatment.

Epinephrine sulphonate (or epinephrine sulphonic acid):
NMT 7.5% wrt epinephrine.

Comment:
The quantity present in the drug product manufactured aseptically is not detectable, but it is detectable in the heat sterilized drug product at about 0.2-0.3mcg/mL..

pH:
2.7 to 5.2.

Comment:
For some unknown reason this USP pH range is very wide, wider than other compendial

anesthetic formulations containing epinephrine (USP Bupivacaine, lidocaine and epinephrine pH 3.3 to 5.5), . Generally for local anesthetics containing epinephrine and an antioxidant (Sulphite or metabisulphite) the pH of the formulation is about 4.2. This pH is corrected to below pH 4 in order to reduce the rate of the reaction of the epinephrine with the metabislphite. In time, during storage of the DP the pH falls due to the formation of sulphuric acid from the oxidation of the metabisulphite/ sulphite.

Particulate matter in injections:
Meets requirements under USP <788>.

Comment:
It is a requirement for solutions for injection and is the same for both processes.

Sterility:
Sterile

Comment:
It is a requirement for solutions for injection and specification is the same for both processes.

Bacterial endotoxins:
Meets USP requirements

Comment:
It is a requirement for solutions for injection and specification is the same for both processes.

Other important parameters not in the USP specifications:

Anti-oxidant:
required to protect the epinephrine from oxidation.

Comments:
All local anesthetics containing epinephrine must contain an anti-oxidant (generally sulphite or metabisulphite), otherwise there is excessive degradation of the epinephrine. The sulphite/metabisulphite reacts with any residual oxygen in solution to form sulphuric acid (which lowers DP pH in time) and with the epinephrine to form epinephrine sulphonic acid. The foregoing reactions are faster and more pronounced when the drug product is heat treated. For example sterilization of the DP at 121 C for 20 minutes causes about 4 to 6% loss of the epinephrine and about 15 to 20% loss of the sulphite/metabisulphite.

As can be seen above, the USP articaine and epinephrine injection has several physical and chemical parameters that are heat sensitive and although both aseptic and terminal sterilization production processes gives a DP within the compendial specifications, from a chemical, physical and microbial point of view, the aseptically produced DP will have more constant characteristics at batch release and during the shelf life.
This is confirmed by the fact that aseptically produced FDA approved articaine with epinephrine has a shelf life of 24 months against 18 months for the equivalent heat sterilized drug product.

Conclusion

Which is the best manufacturing method for injectable drug products?
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 and use an aseptic manufacturing process where heat sensitivity is detected.
The above reasoning is supported by the fact that FDA approved articaine with epinephrine dental anesthetics have a 24 month shelf life when produced with an aseptic process and 18 month shelf life when produced with a terminal sterilization process.

Orabloc (articaine and epinephrine Pierrel) is approved by FDA and EMA agencies and is produced aseptically at an Italian manufacturing site.