

# Sterile Filtration of Budesonide as a Preferred Sterilization Strategy

Budesonide is a highly potent glucocorticosteroid characterized by strong local anti-inflammatory activity and comparatively low systemic bioavailability, primarily as a result of extensive first-pass hepatic metabolism. It is formulated in both sterile and non-sterile dosage forms, enabling targeted treatment of inflammatory disorders affecting the pulmonary system, gastrointestinal tract, and nasal mucosa.

Sterile budesonide formulations are widely supplied as aqueous suspensions for inhalation, typically packaged in single-dose ampoules containing 0.25 mg, 0.5 mg, or 1 mg per 2 mL. Stringent sterility assurance is critical for these products, as administration directly into the lower respiratory tract presents a heightened risk of infection in the event of microbial contamination.

The principal advantages of sterile budesonide formulations include enhanced patient safety, suitability for pulmonary and nebulized delivery, therapeutic effectiveness in vulnerable patient populations, and reduced systemic adverse effects. Collectively, these attributes establish sterile budesonide as both the preferred and indispensable option for inhaled respiratory therapies.

In addition to its established use in nebulized suspensions, sterile budesonide may also be considered for dry powder inhaler (DPI) applications, where control of particle size distribution, purity, and microbiological quality is critical to ensure consistent aerodynamic performance and dose delivery to the lungs. While DPI products are typically manufactured under non-sterile conditions, the availability of a sterile active pharmaceutical ingredient (API) can support enhanced process control and risk mitigation strategies, particularly for sensitive patient populations or advanced formulation designs. The use of sterile budesonide may therefore provide additional advantages during development and manufacturing of inhalation products, without altering the intended therapeutic profile, as well as establishing a higher baseline of quality control, minimizing the bioburden and particle-associated contaminants.

## Overview of Budesonide Sterilization Approaches Described in Patent Literature

Owing to the thermolabile nature and inherent chemical instability of budesonide, multiple sterilization strategies have been described in patent literature to achieve sterility while minimizing degradation and preserving critical quality attributes.

Patented approaches consistently demonstrate that budesonide is poorly tolerant of conventional terminal sterilization methods. Exposure to elevated temperatures, oxygen, ionizing radiation, or mechanical stress results in significant degradation, loss of chemical purity, and disruption of particle size distribution—parameters that are particularly critical for inhalation and nebulized dosage forms.



The most robust and extensively protected strategy described in the patent landscape is wet-mass (moist heat) sterilization. In this approach, budesonide is sterilized in a hydrated state, frequently in the presence of surfactants. Carefully controlled autoclave conditions—such as 121 °C for 20 minutes or 132 °C for 3 minutes—have been shown to limit impurity formation and inhibit particle agglomeration. As a result, moist heat sterilization is well established for nebulized budesonide suspensions and remains strongly supported by patent protection.

Additional patented strategies include sterile filtration of nanoparticulate suspensions, wherein particle size is deliberately reduced to enable passage through sterilizing-grade membrane filters, as well as high-temperature short-time (HTST) processes that achieve sterility through rapid heating and cooling cycles designed to limit thermal exposure.

Optimized dry-heat sterilization approaches appear less frequently in the patent literature and are typically supported by narrowly defined claims. These methods rely on reduced temperatures, extended exposure times, inert (e.g., nitrogen) atmospheres, or rapid heat-cool cycles to mitigate degradation. Despite their technical feasibility, dry-heat approaches offer a limited safety margin. Given budesonide's sensitivity to heat and oxygen, these methods carry an elevated risk of oxidative degradation, impurity formation, and particle agglomeration, and are therefore considered less robust from both a technical and regulatory standpoint.

A smaller but distinct niche is occupied by supercritical carbon dioxide (scCO<sub>2</sub>) sterilization. This methodology minimizes oxidative and radiolytic damage while preserving particle size distribution and impurity profiles. Although occasionally characterized as a “cold” sterilization technique, its principal advantage lies in enhanced chemical stability rather than complete avoidance of thermal exposure. scCO<sub>2</sub> sterilization may offer freedom-to-operate in scenarios where autoclave-based sterilization is unsuitable.

Ancillary strategies described in patents include sterile filtration of excipients followed by aseptic incorporation of budesonide into the final formulation. In contrast, irradiation-based sterilization methods, including gamma and electron-beam irradiation, are consistently discouraged due to their association with increased impurity levels and deleterious effects on particle morphology.

Overall, the patent landscape places strong emphasis on the preservation of impurity profiles and particle size distribution, as these attributes are essential for ensuring consistent product performance, therapeutic efficacy, and regulatory comparability.



## Technical Solution: Sterile Filtration as a Preferred Alternative Sterilization Method

Sterile filtration was selected by Curia as the technical solution of choice, as it represents one of the most robust and regulatorily accepted strategies for the manufacture of sterile budesonide active pharmaceutical ingredient (API).

Budesonide exhibits pronounced sensitivity to elevated temperatures, oxidative environments, and other aggressive processing conditions, all of which can result in chemical degradation and loss of critical quality attributes. Consequently, sterile filtration was selected in preference to alternative sterilization approaches—such as moist heat, dry heat, irradiation, or gaseous sterilization—in order to preserve both the chemical integrity and physical characteristics of the budesonide API.

In contrast to sterilization methods that rely on thermal or chemical inactivation, sterile filtration achieves sterility through the physical removal of microorganisms, thereby minimizing molecular stress on the API. When terminal sterilization is not feasible due to product instability, sterile filtration is widely recognized as the preferred approach for the manufacture of sterile APIs and is fully aligned with regulatory expectations. At Curia, this process is performed at a dedicated sterile manufacturing facility.

The manufacturing process comprises dissolution of the API, followed by controlled bioburden reduction and final sterilization using a validated sterilizing-grade 0.22 µm membrane filter under Grade A (ISO 5) aseptic conditions to ensure effective microbial removal.

Following sterile filtration, the resulting sterile solution is converted into solid API via aseptic crystallization. The solid is subsequently isolated and dried using sterile solid-liquid separation equipment. Where required, the API may undergo further aseptic milling and final packaging. All manufacturing operations are conducted under strictly controlled aseptic conditions and are supported by validated media fill studies and a comprehensive environmental monitoring program, ensuring a high level of sterility assurance throughout the entire process.

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