# Sterilization using Supercritical Fluids

## Recent Developments in Sterilization, Disinfection, and Medical Cleaning Using Compressed Carbon Dioxide

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Supercritical fluids, most notably carbon dioxide, have been investigated thoroughly as a platform for destroying hazardous pathogens, with applications in medical sterilization and disinfection as well as food pasteurization. Research has been directed at both fundamental understanding and commercial development. Diverse applications, ranging for example from reusable medical instruments to pharmaceutical ingredients to implantable tissues, involve an exceedingly broad variety of pathogens and an equally broad variety of materials and morphologies. Successful commercial development requires understanding of the biological mechanisms of sterilization, engineering phenomena including mass transport, and materials science and engineering. These considerations, along with economic and regulatory concerns, all play a role in determining feasibility of application of supercritical fluids to a given medical or pharmaceutical product.

This report summarizes current knowledge concerning important mechanisms, engineering phenomena, and materials science underlying supercritical fluid sterilization. The goal of this review is to enable those in the field to identify opportunities for commercializing the technology, and to recognize the various challenges and needs unique to different combinations of pathogen and product.

## Supercritical $CO_2$ Sterilization of APIs: Is SC $CO_2$ a Penetrating Sterilant? Guidelines for Scale-up

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The most common methods of sterilization are heat, irradiation, and chemical agents such as ethylene oxide and hydrogen peroxide. One key advantage of heat and irradiation is that they are penetrating steriliants. Consequently, for parenteral drug products, aseptic crystallization is not required for a drug substance which has poor solubility in water and therefore cannot be sterile filtered. Chemical agents, however, are considered surface sterilinats, and thus, aseptic crystallization of the water-insoluble drug substance is required to assure that the inside of the crystal is sterile. In order to evaluate if Supercritical $CO_2$ (SC $CO_2$) can be considered a penetrating sterilant, laboratory studies were performed in which the drug substance was crystallized in the presence of *Geobacillus stearothermophilus* spores to obtain an average population of about $10^6$ colony forming units (CFUs) per gram of powder. The contaminated powder was then isolated, dried and sterilized by SC $CO_2$. It was demonstrated that the reduction in viable count ranges from 92.2% to 100% depending on the particle size distribution of the API.

Supercritical $CO_2$ (SC $CO_2$) has been successfully used by several groups in the sterilization of medical equipment, implants, allografts, and tissues primarily at a lab scale. Recently, we have also demonstrated that SC $CO_2$ can be used in the sterilization of Active Pharmaceutical

Ingredients (APIs) at the lab scale to achieve $10^{-6}$ sterility assurance level (SAL). In order to transfer the SC $CO_2$ sterilization process to production, it is essential to understand the impact of process parameters on the efficacy of sterilization as well as the criteria for scaling up these parameters. For intensive parameters such as temperature and pressure, the ranges established in the lab scale equipment should apply to the production scale equipment. For extensive parameters such as mixing and flow, the scale up criteria followed for chemical processes, geometric and dynamic similarities, should also apply. In this paper, we discuss the guidelines for scaling up the SC $CO_2$ sterilization from a 1-liter to a 500-liter high pressure vessel.