



Processing Prior to Filling and Sealing Operation in Sterile Manufacturing

The purpose of this article is to supplement the guidance provided in this document with information on products regulated by CBER or CDER that are subject to aseptic processing from early in the manufacturing process, or that require aseptic processing through the entire manufacturing process, due to their inability to be sterilized. The scope of this appendix includes aseptic processing activities that take place prior to the filling and sealing of the finished drug product. Special considerations include those for:

A) Aseptic processing from early manufacturing steps

Due to their nature, some products undergo aseptic processing at some or all manufacturing steps preceding the final product closing step. There is a point in the process after which a product can no longer be rendered sterile by filtration, and the product is handled aseptically in all subsequent steps. Some products are formulated aseptically because the formulated product cannot be sterilized by filtration. For example, products containing aluminum adjuvant are formulated aseptically because once they are alum adsorbed, they cannot be sterile filtered.

When a product is processed aseptically from early steps, the product and all components or other additions are rendered sterile prior to entering the manufacturing process. It is critical that all transfers, transports, and storage stages are carefully controlled at each step of the process to maintain sterility of the product.

Procedures that expose the product or product contact equipment surfaces to the environment, such as aseptic connections, should be performed under unidirectional airflow in a Class 100 environment. The environment of the room surrounding the Class 100 environment should be class 10,000 or better. Microbiological and particulate monitoring should be performed during operations. Microbial surface monitoring should be performed at the end of operations, but prior to cleaning. [Personnel monitoring](#) should be performed in association with operations.

Process simulation studies should be designed to incorporate all conditions, product manipulations, and interventions that could impact on the sterility of the product during manufacturing. The process simulation, from early process steps, should demonstrate that

controls over the process are adequate to protect the product during manufacturing. These studies should incorporate all product manipulations, additions, and procedures involving exposure of product contact surfaces to the environment. The studies should include worst-case conditions such as maximum duration of open operations and maximum number of participating operators. However, process simulations do not need to mimic total manufacturing time if the manipulations that occur during manufacturing are adequately represented.

It is also important that process simulations incorporate storage of product or transport to other manufacturing areas. For instance, there should be assurance of bulk vessel integrity for specified holding times. The transport of bulk tanks or other containers should be simulated as part of the media fill. A for more guidance on media simulation studies. [Process simulation studies](#) for the formulation stage should be performed at least twice per year.

B) Aseptic processing of cell-based therapy products (or of products intended for use as cell based therapies)

Cell-based therapy products represent a subset of the products for which aseptic manipulations are used throughout the process. Where possible, closed systems should be used during production. Cell-based therapy products often have short processing times at each manufacturing stage, even for the final product. Often, it is appropriate for these products to be administered to patients before final product sterility testing results are available. In situations where results of final [sterility testing](#) are not available before the product is administered, additional controls and testing should be considered. For example, additional sterility tests can be performed at intermediate stages of manufacture, especially after the last manipulation of the product prior to administration. Other tests that may indicate microbial contamination, such as microscopic examination, gram stains, and endotoxin testing should be performed prior to product release.

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