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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, FOOD AND DRUG ADMINISTRATION

GUIDELINE ON STERILE DRUG PRODUCTS
PRODUCED BY ASEPTIC PROCESSING

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I. PURPOSE

This guideline informs interested persons on certain practices and procedures for the preparation of sterile drug products by aseptic processing that constitute acceptable means of complying with certain sections of the Current Good Manufacturing Practice (CGMP) regulations for drug products (Title 21 Code of Federal Regulations, Parts 210 and 211). For biological products regulated under 21 CFR Parts 600 through 680, it should be noted that sections 210.2(a) and 211.1(b) provide that where it is impossible to comply with the applicable regulations in both Parts 600 through 680 and Parts 210 and 211, the regulation specifically applicable to the drug product in question shall apply. Therefore, the sterility testing of biological products, and the culture media employed for such testing, must conform to the requirements under section 610.12.

II. INTRODUCTION

This guideline is issued under 21 CFR 10.90, and as such, it states principles and practices of general applicability that are not legal requirements but are acceptable to the Food and Drug Administration (FDA). A person may rely upon this guideline with the assurance of its acceptability to FDA, or may follow different procedures. When

different procedures are chosen, a person may, but is not required to, discuss the matter in advance with FDA to prevent the expenditure of money and effort on activity that may later be determined to be unacceptable.

This guideline may be amended from time to time as the agency recognizes the need through its regulatory efforts and through comments submitted by interested persons.

There are certain differences between the production of sterile drug products by aseptic processing and by terminal sterilization. Terminal sterilization usually involves filling and closing product containers under conditions of a high quality environment; the product, container, and closure are usually of a high microbiological quality but are not sterile. It is important that the environment in which filling and closing is achieved be of a high quality in order to minimize the microbial content of the product and to help assure that the subsequent sterilization process is successful. The product in its final container is then subjected to a sterilization process--usually using heat or radiation. In aseptic processing, the drug product, container, and closure are subjected to sterilization processes separately and then brought together. Because there is no further processing to sterilize the product after it is in its final container, it is critical to the maintenance of product sterility

that containers be filled and closed in an environment of extremely high quality. In addition, there are usually more variables attendant to aseptic processing than to terminal processing, a factor that can make it more difficult to attain a high degree of assurance that the end product will be sterile. For example, before aseptic assembly, different parts of the final product may have been subjected to different sterilization processes -- such as dry heat for glass containers, steam under pressure for rubber closures, and filtration for a liquid dosage form -- each requiring thorough validation and control, each with the possibility of error. (For the terminally sterilized drug product, on the other hand, there is generally only one sterilization process, thus limiting the possibilities for error.) Furthermore, any manipulation of the sterilized dosage form, containers, and closures immediately prior to aseptic assembly involves the risk of contamination and thus must be carefully controlled.

These processing differences have led to several questions on aseptic processing regarding what FDA believes are acceptable ways of complying with certain sections of the CGMP regulations for drug products. The sections most frequently questioned concern buildings and facilities, components, containers/closures, production time limitations, validation, laboratory controls, and sterility testing. Because most of the questions have concerned process validation in

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