Guidance for FDA Staff

Compliance Policy Guide
Sec. 280.110 Microbiological Control Requirements - Licensed Anti-Human Globulin & Blood Grouping Reagents

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U.S. Department of Health and Human Services
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Contains Nonbinding Recommendations

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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the telephone number listed on the title page of this guidance.

I. Introduction:

This guidance represents the Food and Drug Administration's (FDA's) current thinking on the microbiological control requirements for Anti-Human Globulin (AHG) and Blood Grouping Reagents (BGR). It is intended for FDA personnel. This guidance was revised due to the amendments of the referenced regulations and minor changes needed in order to update the guidance.

This document supersedes Microbiological Control Requirements – Licensed Anti-Human Globulin & Blood Grouping Reagents, August 14, 2000.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. Background:

The Quality System Regulation found at Title 21 of the Code of Federal Regulations Part 820 (21 CFR Part 820) applies to the manufacturing process for in vitro diagnostic products (IVDs). IVD products regulated by Center Biologics Evaluation Research (CBER), including AHG and BGR, may have additional manufacturing requirements as a condition of licensure based on the biologics regulations found in 21 CFR Parts 600-660.

IVDs are classified into three major categories based on microbiological control: (1) IVDs labeled as sterile; (2) IVDs that are microbiologically controlled, but are not labeled as sterile;

and (3) IVDs that are not microbiologically controlled. The level of microbiologic control necessary for the manufacture of a specific IVD is established by the manufacturer's process validation studies in accordance with 21 CFR 820.75 and established production and process controls in accordance with 21 CFR 820.70. Most, if not all, IVDs regulated by CBER fall into the category of microbiologically controlled products, including BGR and AHG.

III. Policy:

The requirement for sterility for biological products is found in 21 CFR 610.12; however, there is a specific exception to the test for sterility for AHG and BGR [21 CFR 610.12(h)(1)]. The biologics regulations describe additional standards for licensed BGR (21 CFR 660.20) and AHG (21 CFR 660.50). CBER amended these biological regulations on December 12, 2000 because: (1) the original intent of the standard did not include aseptic processing; (2) the manufacturers do not claim these products as sterile on the product labels; (3) quality checks are required for the end users of licensed IVDs [21 CFR 606.65(c)]; (4) all BGR and AHG contain preservatives; and (5) historically, CBER has not requested sterility requirements during the license application review of these products. Therefore, unless specified in the license application, CBER does not expect AHG and BGR to be manufactured under aseptic conditions; however, they should be manufactured under conditions such that the microbial level will not adversely impact product performance.

IV. Regulatory Action Guidance:

Investigators should not cite a manufacturer of BGR or AHG on the FDA Form-483 for not following aseptic processing procedures unless: (1) the product is labeled as sterile; (2) aseptic processing is required as part of their license; or (3) the firm is not following its own manufacturing SOPs. Manufacturers should develop the process control procedures necessary to ensure the product meets its specifications. Investigators should verify that the manufacturer has established appropriate specifications and validated the process control procedures, including those environmental conditions that could have an adverse effect on product quality. Investigators should consult with CBER's Office of Compliance and Biologics Quality, Division of Inspections and Surveillance if they have any questions regarding the requirements for a particular firm.

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