This guidance was written prior to the February 27, 1997 implementation of FDA's Good Guidance Practices, GGP's. It does not create or confer rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. This guidance will be updated in the next revision to include the standard elements of GGP's.

Guideline for the Manufacture of In Vitro Diagnostic Products

Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance

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PREFACE

The Food and Drug Administration (FDA) often formulates and disseminates guidelines about matters which are authorized by the laws enforced by the Agency. Accordingly, FDA is making available this guideline. This guideline is intended to be used in conjunction with the current Good Manufacturing Practice (CGMP) regulation (§21 CFR 820); the Labeling for In Vitro Diagnostic Products regulation (§21 CFR 809.10), and the "Guideline on General Principles of Process Validation." It is also intended to be used in conjunction with the interpretations published in the "Device Good Manufacturing Practices Manual," Medical Device GMP Guidance for FDA Investigators Manual," and the "GMP Workshop Manual for Sterile Medical Devices."

The notice of availability of the draft guideline stated that it would be issued under §21 CFR 10.90(b), which provides for the use of guidelines to establish procedures or standards of general applicability that are not legal requirements but that are acceptable to the Agency. The Agency is now in the process of considering whether to revise §21 CFR 10.90(b). Although that decision making process is not yet complete, the Agency has decided to publish this guideline. However, this notice and the final guideline are not being issued under the authority of §21 CFR 10.90(b), and the final guideline, although called a guideline, does not operate to bind FDA or any other person in any way.

The Agency advises that this final guideline represents its current position on the requirements of the CGMP regulations for in vitro diagnostic products. The guideline may be useful to manufacturers of in vitro diagnostic products. A person may also choose to use alternate procedures even though they are not provided for in the guideline. If a person chooses to depart from the practices and procedures set forth in the final guideline, that person may wish to discuss the matter further with the Agency to prevent an expenditure of money and effort on activities that may later be determined to be unacceptable by FDA. This guideline does not bind the Agency, and it does not create or confer any rights, privileges, or benefits for or on any person.

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Guideline for the Manufacture of In Vitro Diagnostic Products

1.0 SCOPE

In vitro diagnostic products (IVDs), as defined in §21 CFR 809.3(a), are those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. These products are devices as defined in Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act), and may also be biological products subject to Section 351 of the Public Health Service Act.

This guideline is applicable to manufacturers of all in vitro diagnostic reagents and systems, but is not intended to apply to manufacturers of IVD instrumentation. As such, this guideline applies to clinical chemistry and clinical toxicology devices, hematology and pathology devices, and immunology and microbiology devices.

This guideline provides general guidance on the application of the medical device good manufacturing practice (GMP) regulation, §21 CFR Part 820, to processes commonly used in the manufacture of IVDs. It includes methods and procedures for meeting requirements of the medical device GMP regulation. It also provides general guidance on the application of the labeling regulation, §21 CFR 809.10, for these devices. This guideline will be used as a reference by FDA investigators during GMP inspections of manufacturer's facilities. When manufacturers elect not to rely upon this guideline, FDA expects that their choice of procedures and processes will be equivalent to ensure the safety and effectiveness of their IVDs.

This guideline has been issued to address several areas concerning the application of the GMP regulation to IVDs. Foremost, the guideline will assist IVD manufacturers in complying with the GMP regulation and also help ensure uniform application of the GMP regulation by FDA. It is understood that this guideline is an attempt to reduce instances of failure to comply with the GMP regulation as reflected in FDA's experience with legal actions, recalls, results of GMP inspections, and data from the Center for Devices and Radiological Health (CDRH) Device Experience Network (DEN). The importance of GMP compliance for IVDs was expressed by the Microbiology Device Classification Panel which agreed to down classify microbiological culture media from Class II (performance standards) to Class I (general controls) dependant on vigorous implementation of the GMP regulation.

2.0 INTRODUCTION

The reliability of IVDs is important for accurate diagnosis of a disease or condition and for patient management. Some uses of these products include: diagnosis, screening, therapeutic drug monitoring, collecting epidemiological information, monitoring a course of disease, and antimicrobial susceptibility testing. The failure of an IVD to function as intended, or as stated in the labeling, may result in misdiagnosis and subsequent incorrect, insufficient, unnecessary, or delayed treatment. Consequences to the patient may vary from minimal or nonexistent to serious or life threatening, depending on various factors including the patient's condition and the clinical significance of the diagnostic test. One aspect of the significance or "clinical value" of a specific diagnostic test is whether it is the major means of diagnosis, or whether it is used in conjunction with, or confirmed by, other diagnostic tests along with a physician's evaluation of patient symptoms. A diagnostic test is typically the sole method of diagnosis only when there are no other symptoms or conditions to assist in diagnosis.

IVD reagents and systems include those used in hospitals, clinical laboratories, satellite medical facilities, physician's offices, and in the home by consumers. Depending on the type of facility where a test is performed, the user may or may not have training in laboratory methods and techniques.

3.0 APPLICATION OF THE REGULATIONS TO IVDs

The requirements for manufacturers of IVDs are described in §21 CFR 809. The special labeling requirements for these products are identified in Subpart B - Labeling, §21 CFR 809.10. These labeling regulations also specify the stability study and expiration dating requirements for IVDs. Manufacturers must also comply with Subpart C - Requirements for Manufacturers and Producers, §21 CFR 809.20. This subpart requires compliance with the GMP regulation found in Part 820. IVDs are required to be manufactured in accordance with all applicable GMP requirements.

The medical device GMP regulation is an umbrella regulation covering all devices, unless exempted. The GMP regulation specifies quality assurance objectives and principles rather than exact methods, because not all methods are applicable to all processes. It is left to the judgment of each manufacturer to develop methods appropriate to their specific devices and manufacturing processes. To assist manufacturers in developing appropriate methods, this guideline will identify some of the controls implemented for IVDs to ensure the suitability of the product for its labeled and/or intended uses. These are by no means the only controls that may be used to comply with the GMP regulation. IVD manufacturers may use any appropriate method of manufacturing to ensure the quality of IVDs, as long as they have demonstrated by validation that the methods are suitable for their products.

3.1 PRODUCT AND PROCESS SPECIFICATIONS

There are a number of sections of the GMP that require manufacturers to establish product and process specifications. Section 820.100 requires that written manufacturing specifications and processing procedures be established, implemented, and controlled to assure that the IVD conforms to its original design or any approved changes in that design. Section 820.100(a)(1) of the GMP regulation requires that manufacturers of medical devices establish specifications for all devices, including the components, packaging, and labeling. Section 820.100(b) requires that where deviations from device specifications could occur as a result of the manufacturing process itself, there are written procedures describing any processing controls necessary to assure conformance to specifications. Section 820.181(a) requires that the device master record contain device specifications including appropriate drawings, composition, formulation, and component specifications. Section 820.181(b) requires production process specifications including the appropriate equipment specifications, production methods, production procedures, and production environment specifications. Section 820.181(c) requires quality assurance procedures and specifications including the quality assurance checks used and the quality assurance apparatus used. Section 820.181(d) requires packaging and labeling specifications including the methods and processes used. The following is a means of complying with these GMP sections for establishing product and process specifications for IVDs.

An IVD is typically defined during the preproduction process. Some parameters considered are physical, chemical composition, and microbiological characteristics. Performance characteristics such as accuracy, precision, specificity, and sensitivity are also considered. Once the IVD is properly defined, the parameters and characteristics are translated into written specifications.

These established specifications will determine the appropriate production and process controls such as mixing and filling processes, sterilization, or lyophilization needed to manufacture the IVD. The specifications established for the IVD will also determine the appropriate environmental controls needed, in conjunction with the manufacturing process, to ensure that product specifications are consistently met.

The specifications for the product, the manufacturing process, and the environment are maintained as part of the device master record (DMR), as required by § 820.181.

3.1.1 Product Specifications

Parameters typically considered for IVDs are the product's physical characteristics, chemical composition, microbiological quality, and performance characteristics. This section focuses on two of these; performance characteristics and microbiological characteristics, and provides a means of defining these product specifications.

Performance characteristics define analytical performance, and include characteristics such as accuracy, precision, sensitivity, specificity, purity, and identity. The consistency of these product attributes is not "tested into" the finished product, but is achieved through the establishment of adequate product specifications; and by ensuring that these specifications are met through product and process design, process validation, process water controls, manufacturing controls, and finished product testing.

Microbiological quality for IVDs can be classified into three major categories: <u>IVDs which are sterile</u>; <u>IVDs which are microbiologically controlled</u>; and, <u>IVDs which are microbiologically uncontrolled</u>.

IVDs are labeled as sterile if sterility of the product is needed for performance, effectiveness, and/or reliability. The product specifications for sterile IVDs include the sterility assurance level (SAL) necessary for the product.

At the other end of the spectrum are IVDs which are microbiologically uncontrolled. These are IVDs which contain components that are either toxic to microorganisms or do not support the growth of microorganisms. Even though microorganisms do not live or multiply in the IVD, the remains or byproducts of any microorganisms are shown not to adversely affect product performance.

Between the two extremes are IVDs that support microorganism life and growth, and the IVD may contain levels of microorganisms. During the preproduction process, a determination is made as to whether these levels could adversely affect product performance. A determination is also made as to whether a certain type (genus, species) of microorganism can adversely affect product performance. Whether the remains (cell walls) or byproducts (biochemicals) of these microorganisms can adversely affect product performance is also determined. When the IVD is stored and used, according to its labeling, and product performance is found to be adversely affected by certain levels, certain types, remains, or byproducts of microorganisms; then, specifications are established to limit the microorganisms to a level that will not have an adverse impact on product performance. In cases where adequate preproduction design has not been performed for this category of IVDs, a retrospective study using adequate information such as product test data, complaint file analysis, trend analysis, bioburden studies, and process control data, along with an examination of the buildings, equipment, employee technique, and clothing requirements, may be capable of showing whether the presence of microorganisms in the IVD can or cannot adversely affect product performance.

The July 1988 document titled "Microbial Load Considerations for Prepared Culture Media Products" prepared jointly by the Health Industry Manufacturers Association (HIMA) and the Association of Microbiological Diagnostics Manufacturers (AMDM) contains applicable supplemental information(1). This document focuses primarily on tissue culture and microbiological media.

3.1.2 Process Specifications

As stated previously, the important characteristics for IVDs are the product's chemical composition, microbiological quality, and its physical and performance characteristics. This section focuses on microbiological characteristics for IVDs and provides a means of defining process specifications.

Appropriate process specifications are established to ensure that IVDs which are labeled sterile are indeed manufactured under appropriate conditions and controls which will result in a sterile product. Sterile IVDs may be produced by either terminal sterilization or by aseptic processing which may include filtration and/or the use of microbiological inhibitory systems. A sterility assurance level (SAL) commensurate with the need for safe and effective performance of the IVD is established as part of the process specifications. A well designed and established manufacturing process is capable of achieving a SAL of at least 10^{-3} for aseptically filled products and at least 10^{-6} for terminally sterilized products. However, a SAL of 10^{-6} may not be appropriate for some terminally sterilized products which are heat labile and where product performance would be adversely affected.

Appropriate process specifications are established to ensure that microbiologically uncontrolled IVDs are manufactured under appropriate conditions and controls which will result in a product which consistently meets all of its specifications. Normally, the process conditions and controls for this category of IVDs are less stringent than those for IVDs which are labeled as sterile and for microbiologically controlled IVDs. These IVDs require minimal or no specific microbiological controls during processing. Filtration or other processes may be employed to ensure an aesthetically acceptable product. Nevertheless, process conditions and controls, along with adequate specifications, are established.

Appropriate process specifications are established to ensure that microbiologically controlled IVDs are manufactured under appropriate conditions and controls which will result in a product which consistently meets all its specifications. A microbiological assurance level (MAL) commensurate with the need for safe and effective performance of the IVD is established as part of the specifications. A well designed and established manufacturing process is capable of achieving a specified MAL. A MAL is specified for each product which, if exceeded, would adversely affect product performance.

Microbiological control is accomplished by filtration, by using preservatives, and/or by implementing appropriate process controls:

A) Some IVDs are filtered to remove certain, but not necessarily all, microorganisms; and testing assures that these specified microorganisms have been removed from the final product. Finished product testing provides reasonable assurance that the presence of other microorganisms will not adversely affect patient sample test results, and that the IVD will perform in a safe (from the user's perspective) and effective (from the patient's perspective) manner. These IVDs may be labeled as "filtered," "sterile filtered," and "sterilized by filtration." (Refer to Appendix II, Definitions).

B) Some IVDs contain low levels of microorganisms which are controlled through the use of microbiological inhibitory systems such as antibiotics, preservatives, pH control, or antisera. When preservatives or antibiotics are used, known amounts are added which effectively inhibit microorganism growth throughout the product's shelf life and use according to labeling. Refer to Section 3.8, Finished IVD Inspection and Testing, for further discussion.

C) Some IVDs that contain microorganisms cannot be filtered, nor contain microbiological inhibitory systems, because product performance would be adversely affected.. Consequently, microorganisms are likely to be present in the product. The allowable level of contamination that will not adversely affect product performance throughout the IVDs shelf life is determined, and appropriate specifications and accept/reject criteria are established to ensure this level is not exceeded at the end of production and during controlled storage. Depending on the specific type of product, specifications usually address batch contamination (percent contamination of a lot throughout its labeled shelf life) or contamination per unit (slide, plate, etc.). Typically, these microbiologically controlled IVDs are manufactured by designing a manufacturing process which limits the presence of microorganisms; and, by controlling the contamination of product components through sterilization, aseptic technique, or filtration. In addition to limiting the amount of microorganisms present, some IVDs may be capable of having only specific types of microorganisms which would not adversely affect product performance. In this case, the specific types of microorganisms are identified and limited according to the product's established specifications which assure that product function is not adversely affected through its expected shelf life and use according to labeling.

3.2 PROCESS VALIDATION

Section 820.5 requires that every finished device manufacturer prepare and implement a quality assurance program that is appropriate to the specific device manufactured. Section 820.3(n) defines quality assurance as all activities necessary to assure and verify confidence in the quality of the process used to manufacture a finished device. Section 820.100 requires that written manufacturing specifications and processing procedures be established, implemented, and controlled to assure that the device conforms to its original design or any approved changes in that design. Section 820.100(a)(1) requires that procedures for specification control measures be established to assure that the design basis for the device, components, and packaging is correctly translated into approved specifications. These four GMP sections establish the requirements for process validation, as stated in FDA's "Guideline on General Principles of Process Validation."(2) It is suggested that this guideline be consulted when establishing validation procedures. The following are a means of meeting process validation requirements.

Process validation is defined as establishing documented evidence which provides a high degree of assurance that a specified process will consistently produce a product meeting its predetermined specifications and quality attributes. The process is validated using accepted methods after defining the manufacturing process, including the equipment, the environment in which the operation is to be performed, and the quality assurance controls to be applied. When validating a process, the interaction of all systems is evaluated. Process validation applies to all three microbiological categories of IVDs to ensure that a specified process will consistently produce an IVD which meets all specifications and quality attributes. Validation may be prospective or retrospective, or a combination of both.

All new IVDs and/or processes are to be prospectively validated. Prospective validation is performed for IVDs which are labeled as sterile because of the limitations of finished product sterility testing. Prospective validation is also used for microbiologically controlled IVDs and for microbiologically uncontrolled IVDs because of the limitations of statistical sampling.

Retrospective validation is the examination and evaluation of historical data for the process and the product. Where retrospective validation is planned for all or part of the manufacturing process for an old product, preproduction process development, qualification, documentation, and process data collection are carefully and appropriately done. Retrospective validation is not used to justify a bad system or a bad product. It is intended to be used to examine a system objectively and determine whether it is acceptable, whether changes need to be made, or whether the entire process needs to be replaced.

In some cases, retrospective validation may be used for IVDs which have been marketed without sufficient premarket process validation. It may be possible to validate, in some measure, the adequacy of the process by examination of accumulated test data and manufacturing records. Retrospective validation encompasses: a review of the process design; determining whether adequate specifications have been established and met for each processing variable; determining whether adequate test methods and sampling plans were established, and adequate sampling and testing was performed to provide a significant data base; and, determining whether adequate procedures are in place. Process and product test data may be useful only if the methods and results are adequate and specific. Specific results can be statistically analyzed and a determination can be made of what variance in data can be expected. Records which describe each process variable are maintained. When test data is used to demonstrate conformance to specifications, the test methodology is qualified to ensure that test results are objective and accurate. Retrospective validation can be used for microbiologically controlled IVDs and for microbiologically uncontrolled IVDs.

3.3 PRODUCTION AND PROCESS CONTROLS

Section 3.2, Process Validation, outlines the GMP sections applicable to process validation (§ 820.100(a)(1)). FDA has interpreted the GMP regulation to require validation of manufacturing processes such as sterilization, lyophilization, filtration, and filling processes. Section 820.100(a)(2) requires that specification changes be subject to controls as stringent as those applied to the original design specifications of the device. Section 820.100(b)(1) requires that where deviations from device specifications could occur as a result of the manufacturing process itself, there shall be written procedures describing any processing controls necessary to assure conformance to specifications. Complying with these GMP sections involves validation and revalidation, and establishing processing controls, for sterilization and microbiological reduction techniques, lyophilization, filtration, and filling processes.

3.3.1 Sterilization and Microbiological Reduction Techniques

Sterilization of product, containers, closures, and the equipment used in production is accomplished by a variety of different methods or processes. These same techniques can be used to reduce the microbial load of microbiologically controlled products. In general, the sterilization and microbial reduction processes used in the production of IVD products are steam, ethylene oxide, radiation, and dry heat, along with appropriate process controls. The CDRH has published responses to common questions regarding sterilization processes(3). These processes are used in manufacturing IVDs which are labeled sterile; sterilizing components for either IVDs which are labeled sterile, or microbiologically controlled IVDs; and, reducing the microbial load for either microbiologically controlled IVDs or microbiologically uncontrolled IVDs.

Saturated steam is used for terminal sterilization or for reducing a microbial load. Guidance for the qualification of autoclaves and validation of autoclave cycles is found in the Parenteral Drug Association (PDA), Technical Monograph No. 1: "Validation of Steam Sterilization Cycles."(4)

Ethylene oxide (EO) has some limited uses in IVD manufacturing. The Association for the Advancement of Medical Instrumentation (AAMI) "Guideline for Industrial Ethylene Oxide Sterilization of Medical Devices" contains guidance for the qualification of sterilization chambers and for the validation of EO process cycles(5).

Gamma radiation also has some limited uses in IVD manufacturing and is usually a contracted service. The AAMI "Process Control Guidelines for Gamma Radiation Sterilization of Medical Devices" contains guidance for gamma radiation processes(6).

Dry heat has some limited uses in IVD manufacturing. The PDA Technical Report for "Validation of Dry Heat Processes Used for Sterilization and Depyrogenation" contains guidance for the qualification and validation of dry heat chambers and processes(7).

3.3.2 Lyophilization

Lyophilization may adversely affect the sterility or microorganism load, potency, activity, and stability of the final product if not properly validated and controlled. The lyophilization process is validated as part of overall process validation. The general principles of process validation found in the FDA process validation guideline apply(2). Specific guidance is found in several technical references(8)(9). A basic understanding of the process provides insight into the variables which need to be controlled.

Lyophilization essentially consists of the following: freezing an aqueous product; evacuating the lyophilization chamber, usually below 0.1 torr (100 microns Hg); subliming ice on a cold condensing surface at a temperature below that of the product (the condensing surface is within the chamber or in a connecting chamber or unit); and, introducing heat under controlled conditions to dehydrate the product.

Equipment is qualified to show it is capable of monitoring and controlling the lyophilization process parameters such as pressure, vacuum, temperature, and time so that the desired moisture levels in the final product are reproducible. Qualification of the lyophilizer includes calibration of gauges such as thermometers, timers, and recorders, and also includes a "vacuum hold" to test for chamber leaks which could adversely affect the final product.

As stated previously, some IVDs are filtered and then aseptically filled into sterile containers. Because the containers usually remain open during the drying process, air is evacuated, and clean air or inert gas, such as nitrogen, is reintroduced into the chamber during the lyophilization process to prevent contamination. The product is protected from contamination during transfer from the filling area to the lyophilizer, while in the freeze-drying chamber, and at the end of the drying process until the containers are sealed. For sterile and microbiologically controlled IVDs, the exhaust and input ports of the chamber have terminal sterilizing filters so that contaminants do not enter the chamber. The filters are periodically replaced, or periodically sterilized and integrity tested. Similar controls are instituted for other IVDs to ensure that the production process does not introduce contaminants which adversely affect product performance.

The final moisture content of the product is specified. If testing is performed as part of process validation, testing on each manufactured lot would not be required as long as the lot is lyophilized within the validated cycle parameters. Failure to maintain an acceptable moisture content may result in a final product that is subpotent, less active, or less stable than labeled.

Adequate cleaning or disinfection of the chamber's internal surfaces including the water condensate drain lines may be necessary. The drains are not connected to sewer lines without atmospheric breaks or backflow prevention equipment.

3.3.3 Filtration

Filtration is used in IVD manufacturing to remove particulates, to sterilize, and to reduce a microbial load. Filtration is frequently used for sterilization or to reduce a microbial load because some IVDs are heat labile. To prevent the reintroduction of particulates or microorganisms, filtration is usually accompanied by dispensing the filtered component or final product into a clean and/or presterilized container within a controlled environment.

The compatibility between the product and the filter is normally determined during validation of the filtration process. Filters are constructed from a variety of different synthetic materials, and assurance is obtained during the validation process that the substrate and solvents used in IVD production do not react with the filter material. Reactions with the filter material can change the filter porosity allowing contaminants to pass, or denature the filter material adding chemical components to the final product which could adversely affect product performance.

Some filtration operations use either pressure or vacuum to force the product through the filter. Filter manufacturers rate their filters to indicate the maximum pressure or vacuum to be applied to the face of the filter. Some IVDs contain macro-molecules such as polypeptides. These viscous products have slower filtration flow rates; therefore, longer filtration times and/or larger membrane areas are required. Appropriate controls are in place to ensure the maximum rating is not exceeded. Filter suitability encompasses the following applicable areas: flow rates, throughputs, sterilizability, extractables, particles, product stability, toxicity, compatibility of product, and pyrogenicity.

Guidelines for validating filters have been published, and may be used when assessing the adequacy of filter validation (10)(11)(12)(13). Filter manufacturers may have already validated their filters for bacterial retention. Some of the more complex validation tests are performed by filter manufacturers or contract laboratories, and the test data applying to the IVD manufactured is accessible to the IVD manufacturer.

Because a filter may contain pores larger than the nominal rating, and the probability of microorganism passage increases as the number of organisms in the filtered material increases, a maximum bioburden is established and the filter is challenged using that bioburden. Pseudomonas diminuta is normally used for challenging a filter's nominal porosity and for simulating the smallest microorganism occurring in production. Once production begins, product bioburden is controlled, and periodic testing ensures that maximum levels are not exceeded. If bioburden limits are exceeded, an investigation is performed to identify and correct the cause.

Terminal filtration of soluble liquid IVDs for purposes of sterilization or microbial reduction involves the use of a terminal bacterial retentive filter, which has a 0.2 micrometer or smaller pore size rating for most products. Membrane filters are rated by absolute pore size, while depth filters are rated by absolute and nominal pore size. Occasionally, for products with high viscosity or high colloidal content that inhibit filtration through 0.2 micrometer filters, it may be possible to exclude certain microorganisms by using 0.45 micrometer filters in series. Filters of 0.45 micrometer porosity or larger are also useful as pre-filters in extending the life of the terminal filter.

Filtration of some IVDs involves the removal of bacteria, yeasts, and molds. Some IVDs are also filtered to exclude specified interfering mycoplasma, rickettsia, and viruses; however, even a

0.1 micrometer filter may not totally remove these contaminants. If filtration does not remove a contaminant which will adversely affect performance, appropriate and adequate process controls are established to prevent the introduction of the contaminant into the component or finished IVD. In the event the prohibited contaminant is detected, appropriate corrective measures are established.

After validating the filtration process, the manufacturing process, and filter for a given IVD or related class of IVDs, other factors are considered to ensure that replacement filters will perform in the same manner. Procedures are established to ensure that replacement filters are installed in accordance with the filter manufacturer's instructions. The failure to install a filter properly is not necessarily reflected in the ability of the filter to pass a pre-use or post-use integrity test. Filter integrity testing is accomplished as often as necessary to ensure the integrity of the filter and adequacy of the process.

3.3.4 Filling Processes

The following is a discussion of filling processes and their validation for IVDs labeled as sterile, microbiologically controlled IVDs, and microbiologically uncontrolled IVDs.

Aseptic processing may be used to process devices intended to be labeled sterile if the process can achieve a SAL of at least 10^{-3}. An aseptically processed product is likely to consist of components which have been maintained in a sterile condition or have been processed by one of the previously described sterilization processes. USP states that aseptic processing is "...designed to prevent the introduction of viable microorganisms into components, where sterile, or once an intermediate process has rendered the bulk product or its components free from viable microorganisms."(14) The container and closure system and applicable production equipment are separately subjected to sterilization processes. Because no further processing occurs after the product is in its final container, production occurs in a controlled environment to maintain product sterility. Manipulation of the product, containers, or closures prior to or during aseptic processing increases the risk of contamination and is controlled as much as possible. Guidance for aseptic processing operations can be found in FDA's "Guideline on Sterile Drug Products Produced by Aseptic Processing."(15)

An aseptic processing area or facility for IVDs labeled sterile typically includes some of the following conditions and controls: non-porous, smooth surfaces on floors, walls, and ceilings which can be sanitized or disinfected easily; gowning areas or rooms with adequate space for personnel, garment storage, soiled garment disposal, and hand washing; adequate separation of personnel preparation rooms from the aseptic room by means of airlocks, pass-through windows for components, supplies, and equipment; and, access limited to authorized personnel(16)(17). Training programs and procedures are developed to ensure that all materials brought into the primary environment have been adequately decontaminated or controlled. Specifications for environmentally controlled areas are contained in the device master record.

HEPA filtered enclosures are used particularly in and over the immediate area of the exposed product. Some aseptic processing of IVDs is performed in a HEPA filtered, unidirectional airflow cabinet. Other IVDs which are potentially infective are processed in HEPA filtered biological safety cabinets which are negative in pressure to the secondary environment to protect the worker and the product.

The production and process controls necessary to produce IVDs labeled sterile are well defined in existing guidelines(15)(18)(19). Similar processes used by manufacturers who do not intend to produce sterile devices or IVDs labeled sterile, but are attempting to achieve a certain level of microbiological control, have not been well defined. However, regardless of the process utilized, it is defined in terms of the desired results and allowable operating parameters. These are translated into written process specifications and maintained in the device master record.

A microbiologically controlled IVD is likely to consist of components which have been processed or maintained with a controlled microbial load. The container and closure systems may also be processed to sterile conditions or conditions that will ensure a low microbial load. Because no further processing occurs after the product is in its final container, production is performed in a controlled environment to prevent an increase in the product's microbial load beyond its design specifications.

A microbiologically uncontrolled IVD does not normally have as stringent controls as those for IVDs which are labeled as sterile or for microbiologically controlled IVDs. Appropriate production and process controls are defined in written specifications and instituted to ensure that each filled unit is capable of meeting its established performance specifications. This includes items such as volume of fill, closure integrity, and prevention of contamination during the filling process which adversely affects product performance.

3.3.4.1 Validation of Filling Processes

Aseptic processes are validated because finished product testing for sterility or contamination has limited usefulness. USP, Section 1211, Aseptic Processing states "Certification and validation of the aseptic process and facility is achieved by establishing the efficiency of the filtration systems, by employing microbiological environmental monitoring procedures, and by processing of sterile culture medium as simulated product. Monitoring of the aseptic facility should include periodic environmental filter examination as well as routine particulate and microbiological environmental monitoring, and may include periodic sterile culture medium processing."(14)

Guidance for the validation of liquid IVD aseptic fill operations is found in PDA Technical Monograph No. 2, "Validation of Aseptic Filling for Solution Drug Products."(18) Guidance for the validation of dry IVD aseptic fill operations is found in PDA Technical Monograph No. 6, "Validation of Aseptic Drug Powder Filling Processes."(19) FDA's "Guideline on Sterile Drug Products Produced by Aseptic Processing" provides detailed guidance on validation by media fills(15). Fill processes used to produce sterile IVDs are validated to a SAL of at least 10^{-3}(18). A sufficient number of containers are filled that will provide a high degree of probability of detecting contaminated units. For example, on a statistical basis, using the formula $P(x>0) = 1-e^{-NP}>0.95$, at least 3,000 units are needed to detect a contamination rate of one in one thousand units (0.1%) with a high degree of probability (95% confidence)(18).

Some aseptically filled IVDs consist of lot sizes smaller than 3,000 units. For these smaller lot sizes, each validation run consists of the maximum lot size produced. However, more than three runs are necessary to achieve a high degree of probability (95% confidence) of detecting a contamination rate of 0.1%. Statistically equivalent rationale is developed for other lot sizes, using the formula for a 95% probability or greater for detecting at least one contaminated unit.

The prospective validation procedures for producing microbiologically controlled IVDs closely parallels the same procedures used for IVDs which are labeled sterile. Validation assures that the intended microbiological assurance level (MAL), or other specification for microbial contamination, is achieved consistently. Unlike validation of an aseptic filling process which is used to produce sterile products, validation of microbiologically controlled filling processes is intended to ensure that each filled unit is within established specifications for microorganism levels.

The prospective validation procedures for producing microbiologically uncontrolled IVDs are not as complex as those for IVDs which are labeled as sterile or for microbiologically controlled IVDs. Rather than determining contamination levels, the operation is validated to ensure that it is capable of filling each unit within a run to meet its established performance specifications. This includes such items as volume of fill, closure integrity, and prevention of contamination during the filling process which adversely affects product performance. Of course, these items are also a concern with microbiologically controlled IVDs and IVDs which are labeled sterile.

Each filling line or filling operation is validated, and sufficient validation runs are performed to ensure results are statistically meaningful and consistent. Usually three separate runs are recognized by industry as adequate(20). The number of validation runs is dependent on the need to demonstrate repeatability of the filling process.

Since sampling plans for finished product testing normally carry some inherent risk of allowing defective lots to be accepted, filling processes are revalidated at predetermined intervals or as necessary to ensure that all processes, procedures, and training programs are still adequate. Some additional reasons for revalidation include: building and equipment changes, personnel changes, environmental specifications being exceeded, positive sterility or microbial limits test results, and the failure of IVD lots to meet specifications. Because of the limits of finished product testing, periodic revalidation is performed even in the absence of apparent changes.

Microbiological media, rather than actual product, is normally used to validate a filling process where the intent is to produce a sterile product or to limit microbial contamination. The media for validation runs is chosen for its capability of supporting the growth of microorganisms previously identified by environmental monitoring and by positive sterility tests. Negative and positive controls are used to ensure the validity of the runs. The growth medium and growth promotion organisms listed in USP are generally acceptable for media validation runs. The filled media units from each run are incubated at a sufficient temperature and time period to detect microorganisms. For product labeled as sterile, this would be 7 or 14 days incubation, depending on the sterility test method employed, and it would be 3 days for microbial limits testing. Where more than one medium or incubation condition is used to detect all potential contaminants, failure or contamination rates are calculated separately for each type of medium utilized during validation, and separate failure or contamination rates are calculated within each medium type when incubated at separate temperatures.

The production environment during filling process validation is challenged at the upper process limits. Some of the items to consider are the number of personnel present in the area, activity levels, temperature, humidity, pressure differentials, and other environmental factors. The duration of each validation and revalidation run encompasses most, if not all, processing steps during actual production operations.

In cases where adequate prospective validation has not been performed for old microbiologically controlled IVDs or old microbiologically uncontrolled IVDs, retrospective validation may be appropriate. Product test data, complaint file analysis, trend analysis, bioburden studies, and process control data, along with an examination of the buildings, equipment, employee technique, and clothing requirements, may be capable of showing whether the presence of microorganisms in the IVD can or cannot adversely affect product performance. A limited prospective validation may be necessary to verify the retrospective study results, especially if inadequate historical data has been collected.

3.4 ENVIRONMENTAL CONTROL

Section 820.46 requires that where environmental conditions at the manufacturing site could have an adverse effect on the fitness for use of a device, these environmental conditions must be controlled to prevent contamination of the device and to provide proper conditions for each of the operations performed pursuant to Section 820.40. This section states that any environmental control system must be periodically inspected to verify that the system is properly functioning, and such inspections must be documented.

Conditions to be considered for control include: lighting, ventilation, temperature, humidity, air pressure, filtration, airborne contamination, and other contamination. Guidance regarding environmental control is found and referenced in Federal Standard 209D "Clean Room and Work Station Requirements, Controlled Environment."(21) The controls needed depend on the type of IVD being produced, and is usually determined, in part, by the product specifications. The following environmental controls apply chiefly to IVDs which are labeled sterile and microbiologically controlled IVDs, but could also apply to microbiologically uncontrolled IVDs. The following are means of complying with the GMP requirements for establishing environmental controls and environmental monitoring for airborne contamination, air pressure, and filtration.

3.4.1 Airborne and Other Contamination

Non-viable particle monitoring is a fast method for indicating area particle contamination levels and is done during validation of the filling process and on a scheduled basis during production. Monitoring is performed at several locations throughout the product exposure period under dynamic conditions.

Reasonable and feasible specifications for non-viable particles are established for controlled environment processing areas. The specifications are verified during process validation as being adequate, and alert and action levels are established. Non-viable particle specifications are established for processing in unidirectional airflow hoods. Because of the possibility of the transfer of contaminants by equipment and employees, particle specifications are also established for the room in which the hood is located. Specifications are established for biological safety cabinets and for the room in which the cabinet is located. Specifications account for the fact that biological safety cabinets utilize room air to create a negative pressure in the hood and a positive pressure in the room.

Viable particle monitoring is performed during process validation and on a scheduled basis during production. Active air samplers are used to quantify the number of microorganisms present in an area. Active samplers include slit-to-agar samplers, sieve samplers, liquid impingement samplers, and centrifugal agar samplers. Passive air samplers, such as settling plates, have limited value in quantitative monitoring, particularly under unidirectional airflow, because microorganisms that do not settle onto plates are not detected. However, they can be valuable in qualitative monitoring: 1) if positioned in critical areas; 2) if they can effectively capture microorganisms; and, 3) if exposure is not so prolonged as to dry the nutrient(22). Environmental monitoring to be considered also includes: touch plate, contact plate, and swab testing of critical surfaces such as floors, walls, ceilings, equipment, utensils, and personnel clothing.

Viable particle monitoring methods, in order to be effective, are shown to be capable of detecting all contaminants of concern. The microbiological culture media used in viable monitoring is incubated at appropriate times, temperatures, and environmental conditions. Any recovered microorganisms are identified to differentiate between normal and incidental contaminants. Although every isolate need not be identified to genus and species, characterization is specific enough: 1) to establish a data base that will demonstrate that cleaning and disinfecting continue to be effective; 2) to establish a relationship between organisms found during prospective validation and finished product testing; and, 3) to determine the resistance of environmental organisms to various sterilization or contamination control processes.

Reasonable and feasible specifications for viable particles are established for controlled environment processing areas. The specifications are verified during process validation as being adequate, and alert and action levels are established. The various processing areas are evaluated, with more stringent limits set in those areas where the product is exposed to the environment, or primary environment, versus secondary environments.

3.4.2 Air Pressure

Air pressure differential specifications are established between primary controlled areas and secondary controlled areas. Quantitatively measurable pressure differential monitoring between the primary controlled areas and secondary controlled areas is performed, and conformance to established specifications is verified. The adequacy of the specifications are verified during process validation, and alert and action levels are established. Controlled environment areas have a positive pressure in relation to areas of lesser control. However, for biological safety cabinets or rooms designed for containment of infectious agents, the primary environment has a negative pressure with respect to the surrounding environment(23).

3.4.3 Filtration

Air filtration is commonly used to help maintain environmental control in a processing area. Reasonable and feasible specifications for non-viable particles are established for controlled environment processing areas. The adequacy of the air filtration system, and the specifications for the system, are verified during process validation.

When controlled environmental conditions are being maintained through the use of HEPA filters, the HEPA filters are certified to be 99.97% efficient in the retention of particles 0.3 micrometer or larger. This is usually done via a DOP test. A certificate of DOP conformance is usually supplied by the filter manufacturer; if not, the IVD manufacturer certifies conformance. Upon installation of the filter and again periodically thereafter (e.g., twice a year), the HEPA filters are integrity tested by the DOP test or equivalent test methods. Whether the frequency of periodic testing is increased or decreased is dependent on the data obtained from previous testing. Periodic quantitative monitoring is performed to ensure HEPA filters are operating within specifications. HEPA filters can enclose entire rooms, can be in a work station, or can be in a unidirectional airflow work station.

In addition to HEPA filters, terminal air filters, used in other controlled environment areas of the firm, are tested upon receipt, or accepted by certificate of conformance, to ensure their retentive capabilities in order to meet the air quality specifications for those areas. Periodic quantitative monitoring is performed to ensure terminal filters are operating within specifications.

Work stations used in the production of infectious agents are certified periodically (e.g., annually) to meet the standards for Type II or Type III Biological Safety Cabinets(23). These certifications establish the filter efficiency and also test the cabinet for leaks that would compromise containment requirements.

3.5 PERSONNEL ATTIRE

Section 820.56(a) requires that where special clothing requirements are necessary to ensure that a device is fit for its intended use, clean dressing rooms are provided. Section 820.25(b) requires that personnel in contact with a device or its environment are clean, healthy, and suitably attired where lack of cleanliness, good health, or suitable attire could adversely affect the device. The following are a means of complying with these GMP sections for determining and establishing personnel attire requirements.

The extent to which clothing procedures and practices are established, validated, and controlled are based on the type of IVD being produced, and are usually determined, in part, by the product specifications.

Where the primary processing environment for IVDs is a controlled environment room or area, appropriate clothing is used to ensure product and process specifications are met. These may include the following items, when appropriate: coveralls, open-face or eyes-only hood, surgical face mask, shoe covers or boots, and surgical gloves. When primary processing is limited to a unidirectional airflow hood or biological safety cabinet, located in a secondary environment, less stringent clothing practices may be employed, such as full-cover lab coat, hair restraint, surgical face mask (if no face shield is present on the hood), and sterile sleeves, and/or gloves.

When aseptic processing is used, proper aseptic gowning practices are essential. Aseptic gowning practices include sterile gloves for handling sterile garments. At the conclusion of the gowning process, these gloves are removed and new sterile gloves put on, or the old gloves are thoroughly cleaned and disinfected. During the gowning procedure, caution is followed to protect sterile garments from contacting non-sterile surfaces which may contaminate the garments. As people generate particles during activity, sleeves and pant legs of the sterile garments are tucked inside the gloves and boot/shoe covers to prevent particles from flushing out of the gown into the environment. Once removed, sterile clothing is not normally reused to enter aseptic areas, unless the practice is validated. Once an employee has moved from a controlled environment to a noncontrolled environment, the employee does not re-enter the aseptic area without regowning, unless the process is validated to show that the employee does not add unacceptable contaminants to the aseptic area.

The use of sterile clothing is the most reliable means of assuring that clothing does not contribute contamination. If sterile clothing is not used, the acceptability of non-sterile clothing is determined during validation. Verification of the effectiveness of all clothing procedures and practices for controlled environment operations is part of validation. Validation includes contact sampling at several sites on each individual immediately after gowning to establish baseline data. Alert and action limits for contamination are established above which it is reasonably expected that an employee is compromising the controlled environment. If this occurs, employee retraining and/or removal from the controlled environment are alternative actions. Employee gowning practices are periodically monitored as part of an ongoing quality assurance program.

3.6 CLEANING AND SANITATION

Section 820.56 requires adequate written cleaning procedures and schedules to meet manufacturing process specifications, and that such procedures are provided to appropriate personnel. The following are means of complying with this GMP section for determining and establishing cleaning and sanitation requirements.

The effectiveness of the cleaning process is determined as part of process validation. Cleaning and disinfecting agents used to clean equipment, floors, and walls need to be effective against the microorganisms which may adversely affect product function. The effectiveness of the cleaning process is verified and documented using swabs or contact plates as part of validation. Once validated, the cleaning process is monitored but may use fewer sampling sites than used during validation. This monitoring may be performed as part of an overall environmental monitoring program.

Acceptable monitoring results would indicate either no viable microorganisms present, or a reduced bioburden which has been demonstrated by process validation to not adversely affect the final product. When results show that the established limits have been exceeded, an investigation is performed to identify the source of the contamination. The cleaning process is repeated as necessary.

Cleaning equipment is stored in a dedicated, controlled area in order to protect the controlled environment area and its equipment from contamination. Water used to prepare cleaning and disinfectant solutions for controlled areas will have low microorganism levels.

3.7 COMPONENTS

GMP requirements for components are stated in § 820.20(a)(2) and § 820.80. Section 820.181(a) requires that the device master record include or refer to the location of component specifications. All raw materials, containers, and closures are considered components. Packaging requirements for IVD containers and closures stated in § 820.181(d) and § 820.130 also apply. The following are several means of complying with these GMP sections for components.

Where deviations from component specifications could result in the device being unfit for its intended use, components are inspected, sampled, and tested for conformance to specifications, or certificates of analysis are obtained from the supplier in lieu of testing upon receipt. Confidence in the validity of certificates is established through experience, historical data, testing, and audits of the supplier. If the device master record contains specifications in addition to those listed in the supplier's certification, then the IVD manufacturer ascertains that the component meets these additional specifications. For those components where a supplier does not perform any testing, or components are manufactured in-house, the IVD manufacturer ascertains that adequate specifications are established and appropriate examinations or tests, as necessary, are performed to ensure these specifications are met. For those components which are intended to be sterile or have a low microorganism load to ensure IVD specifications are met, acceptable levels of bacteria, yeasts, molds, viruses, rickettsia, and mycoplasma, as appropriate, are addressed through established specifications which are then monitored. If any detectable level of endotoxins in the final product would adversely affect product performance, the susceptible components are tested for the presence of endotoxins.

Water is used for a variety of purposes, such as in sterilization systems, preparation of cleaning agents, and in product formulations. Water used in the production of IVDs is as important as any other product component. Water quality is defined as any other component, and the specifications are consistent with the performance characteristics of the final product. Specifications are established for water used in the product and processing. The equipment used to produce the water is qualified and certified. The system is validated to ensure it produces the quality of water it is intended to produce, and the system is routinely monitored to ensure that the quality of the water continues to meet the established specifications. Water for IVD production purposes is usually produced by deionization, distillation, and/or reverse osmosis.

Water used in production may not need to be sterile, except when added aseptically to a sterile product. If the microbial load present in the process water could adversely affect the finished product, then microbiological specification limits are established for the water. An increase in bioburden of water and/or other components may adversely affect the ability of a sterilization process to effectively sterilize a product, or keep a microbiologically controlled IVD within acceptable limits. Thus, monitoring of the microbial load in water is important.

Some IVDs are chemically defined. Therefore, establishing specifications and controlling and testing the ionic and chemical quality of the process water are important in limiting impurities which could adversely affect the IVD.

If detectable levels of endotoxin in the final IVD can adversely affect performance, then it may be necessary to limit gram negative bacteria in the water, establish endotoxin limits, and test the water for endotoxins. Water used in some IVDs may need to have low levels or be free of endotoxins(24). Maximum allowable endotoxin specifications are established from validation data which shows that product performance would not be adversely affected by the permissible limits established.

Points of control for process water systems used in manufacturing IVDs include: 1) proper temperature maintenance in the storage tank; 2) pressure gauges and pressure specifications at various points throughout the system; 3) the absence of dead legs; 4) the absence of in-line bacterial retentive filters (to prevent bacterial build-up on the upstream side, resulting in pyrogen release and bacterial breakthrough) unless their use can be properly validated and monitored; and, 5) the absence of direct sewer connections to the water system, including such situations as hoses attached to water outlets that extend below the top level of sinks, or that contact floors or other non-sanitized surfaces unless they are removed after use. A disinfection and/or sterilization procedure and schedule is established for the entire water system, as necessary, to ensure bioburden specifications are maintained.

3.8 FINISHED IVD INSPECTION AND TESTING

Section 820.20(a)(2) requires that the quality assurance program consist of procedures adequate to ensure proper approval or rejection of all finished devices, and approval or rejection of devices manufactured, processed, packaged, or held under contract by another company. Section 820.20(a)(4) requires that the quality assurance program consist of procedures to ensure that all quality assurance checks are appropriate and adequate for their purpose and are performed correctly. Section 820.160 requires written procedures for finished device inspections to ensure that device specifications are met. The following are means of complying with these GMP sections for finished IVD inspection and testing.

In addition to process validation and in-process controls, adequate sampling and testing of the finished product helps to confirm that manufacturing processes were correctly performed, and that the product will consistently accomplish its intended function within labeled claims, such as accuracy, precision, sensitivity, specificity, sterility, purity, and identity.

Section 820.160 requires that sampling plans for checking, testing, and release of a device be based on an acceptable statistical rationale. Sampling programs are designed and implemented by each manufacturer. They include the establishment of an Acceptable Quality Level (AQL) and selection of a sampling plan that provides an acceptable level of confidence that defective lots, such as those in which the defect rate exceeds the AQL, will be detected and rejected.

There are no simple rules for selecting a value for the AQL, but it is usually product specific and is based on the rate of defects which can be tolerated both by the user and the manufacturer for the specific indicated uses of the IVD. If the IVD has multiple uses, prudence indicates that the value, consistent with the process capability, which produces the best protection for the most sensitive use be selected. Once the AQL is selected, a quality control sampling plan is selected and implemented which will provide an acceptable level of confidence that lots in which the defect rate exceeds the AQL have a suitably high probability of detection and rejection. These plans are based on accepted statistical principles, and documentation is available to support the statistical validity of the plan.

When the selection of the sampling plan is complete, the risks involved in applying the plan need to be understood. This includes such factors as the probability of accepting a lot whose quality is as good or better than the AQL and the risk of accepting a lot with a defect rate which exceeds the AQL. An acceptable plan provides a high degree of confidence commensurate with the significance of the use of the device and the needs of the user. Any sampling plan is valid only if the manufacturing operation is in a complete state of control, as determined through process capability studies or validation.

The sampling plan in use also assures that the samples are representative of the lot. Samples obtained from a filling operation are representative of the lot if they are obtained periodically throughout the filling run, and include the beginning, middle, and end of the filling run. If retesting of the lot is performed, because the initial testing found that the lot failed to meet one or more of its specifications, then the sampling plan being used for the retest accounts for a tightened inspection plan by obtaining a larger number of samples.

Section 820.160 requires that finished devices be held in quarantine or otherwise adequately controlled until released. In most cases, finished IVDs are adequately controlled to prevent release until testing is completed and the products are approved for distribution. FDA allows release of certain finished IVDs before testing is complete if they have a short shelf life, and the length of time required for completion of testing would equal or exceed the IVDs' expiration date. However, if it is found that specifications have not been met upon completion of finished product testing, appropriate corrective action, such as a recall, may be necessary.

Section 820.160 requires that prior to release for distribution, each production run, lot, or batch is checked and, where necessary, tested for conformance with device specifications. It also requires that, where practical, a device shall be selected from a production run, lot, or batch and tested under simulated use conditions. The following are several types of common tests performed on IVDs and suggested ways of complying with this section of the GMP regulation.

Finished product testing generally involves testing a reagent and associated items, or all reagents which are part of a diagnostic system, such as an IVD kit, together to confirm they will function properly as a system. Validated test methods, calibrated equipment, and appropriate traceable standards used in testing are specified to the customer in the product's labeling. Testing assures that each lot is capable of performing accurately with each instrument recommended to the user in the product's labeling. Each lot may not need to be tested on each instrument specified to the user. For example, some of the tests on certain specified instruments can be performed during the product design phase.

Sometimes, it is not possible for a manufacturer to interchange reagents among kits from different lots without adversely affecting performance. If kit reagents are interchanged, the "new" finished device kit may require reevaluation to determine whether it meets labeled performance specifications. If replacing IVD kit reagents with reagents from a different lot can adversely affect product performance, the user is warned of potential problems via labels and other labeling.

The identity of each production lot is verified to ensure compliance with its labeling. Identity tests are performed where visual or other routine inspection or testing alone is insufficient to determine identity. Identity tests in use will depend on the specific product and its labeling claims. Appropriate identity tests that consider the preceding points are designed to distinguish the specific product from any other similar product. In some cases, adequate process validation along with adequate process control may be satisfactory in lieu of identity testing.

Turbidity in a product may not establish that a product is contaminated; however, it may indicate the necessity of investigating the cause, and may be a reason for rejection. The clarity of fluids is not an acceptable proof of sterility because contaminating microorganisms may not always result in turbidity. Further, some products are characteristically turbid; in which case, turbidity would not be a basis for rejection.

Media used to test the final product for sterility testing or microbial limits testing are comparable to those identified in the USP, and are performance tested prior to use in accordance with USP (14). If an IVD contains antibiotics or preservatives, which could mask the presence of microorganisms, the antibiotics or preservatives are inactivated prior to testing in order to detect the potential contaminants.

Some IVDs are their own growth media. Incubation of the finished IVD samples under appropriate conditions and temperatures is performed to detect a wide range of microorganisms. Of course, the finished IVD is also tested to ensure that it supports or inhibits the growth of microorganisms, or exhibits the expected reaction for which it was formulated.

Microbiological inhibitory systems such as antibiotics, preservatives, pH control, or antisera are added to some IVDs to inhibit microbial contamination. The USP states that antimicrobial preservatives "... are used primarily in multiple-dose containers to inhibit the growth of microorganisms that may be introduced inadvertently, during or subsequent to, the manufacturing process. Antimicrobial agents should not be used solely to reduce the viable microbial count as a substitute for good manufacturing practice."(14) While this section in the USP speaks of drug dosage forms, the information is applicable to IVDs. Microbiological inhibitory systems are used for some sterile IVDs to prevent contamination during distribution, storage, or multiple entries into the container by the user. Microbiological inhibitory systems are used in microbiologically controlled IVDs to keep the microbial load at an acceptable level, and to ensure that multiple entry by the customer does not allow the proliferation of microorganisms which could make the product unfit for its intended use. Also, the remains or byproducts of microorganisms may adversely affect product performance. Microbiological inhibitory systems are set at inhibitory levels that will control contamination and yet not adversely affect product performance; and this is determined during preproduction product development and pilot production. Assurance that the microbial levels present in the IVD do not exceed the capability of the microbiological inhibitory system is provided by process validation and periodic product monitoring for microbial limits. Preservative effectiveness levels may be tested using appropriate methods, such as USP, Section 51(14). Other types of microbiological inhibitory systems can be tested using appropriate validated test methods.

3.9 STABILITY STUDIES AND EXPIRATION DATING

Section 820.100(a)(1) requires that procedures for specification control measures be established to ensure that the design basis for the device, components, and packaging is correctly translated into approved specifications. When IVD stability is a design concern, appropriate procedures such as stability studies are conducted and an expiration period, supported by the studies, is established to define the period in which stability is assured. The expiration period is included as part of the product specifications for the IVD and its components, as required by § 820.181(a).

Stability studies for all IVDs are required by Sections 809.10(a)(5) and 809.10(b)(5)(iv). These regulations require that storage instructions be stated on the immediate container label, kit, or outer container label. Storage instructions are required in the product insert for the product in its initial state and for products which are mixed or reconstituted prior to use. Where applicable, storage instructions should include temperature, light, and humidity or other conditions. The immediate container label, and the kit or outer container label, are required by § 809.10(a)(6) to state a means by which the user is assured the IVD meets appropriate standards of identity, strength, quality, and purity at time of use. This assurance can be an expiration date, an observable indication of product alteration, such as turbidity, or instructions for a simple function test. The following are means of complying with these regulations for establishing stability studies and expiration dating.

An expiration date is the usual method used to indicate stability for IVDs. The last date for the product to be used by the customer is defined as the expiration date.

The storage instructions and the expiration period are determined as part of product development for the proposed container/closure system. The device package and shipping container are evaluated as part of this development phase. For example, during product development an IVD labeled for storage at 2° to 8°C was found to be stable for 24 months. Studies were performed by the manufacturer which subjected the IVD to adverse shipping temperatures of -5°C and 37°C for one week each; however, the IVD was stable for only 6 months at 2° to 8°C after being subjected to these adverse shipping conditions. A shipping container was then designed to maintain the IVD product at 2° to 8°C during adverse environmental conditions that might be encountered during shipping to support the 24 month expiration period. This type of design effort supports the type of adequate package design requirements of § 820.130.

Storage instructions for IVDs are required by § 809.10(a)(5) to include reliable, meaningful, and specific test methods such as those in §21 CFR 211.166. Section 211.166 requires sample sizes and test intervals to be based on statistical criteria for each attribute examined to ensure valid estimates of stability and also requires reliable, meaningful, and specific test methods. Performance and identity testing on all IVD reagents and systems is included in the stability testing program. In addition, sterility testing on sterile labeled IVDs, and microbial limits testing on all microbiologically controlled IVDs, is included in the stability testing program. The finished IVD product is held under appropriate conditions to support the expiration period and storage instructions determined during the development phase. These are normally taken from the first three production batches.

Currently, FDA accepts only real time data for supporting an expiration period. The sole exception is free-standing liquid controls which are not part of a kit, but an adjunctive and independent control for another diagnostic kit. If real time data is insufficient to support the full expiration period claimed, FDA may, on a case-by-case basis, accept accelerated data with the understanding that the data will be supported by real time data, or the shelf life adjusted to reflect the real time expiry.

Each IVD is evaluated for additional stability studies if there is any significant change which may affect stability in the manufacturing process or equipment; in the components, including the container/closure system; or, in the shipping container.

3.10 COMPLAINTS AND FAILURE INVESTIGATIONS

Adequate complaint handling systems are required by § 820.198. The following are means of complying with these regulations for maintaining complaints, performing complaint investigations, and performing failure investigations.

A complaint is either a written or oral communication relative to an IVDs' identity, quality, durability, reliability, safety, effectiveness, or performance. A written or oral communication which meets the definition of a complaint must be reviewed, evaluated, and maintained by a formally designated unit. The formally designated unit may be an individual or a designated department. If the formally designated unit decides that the complaint does not need to be investigated, a record must be maintained which includes the reason the complaint was not investigated and the name of the individual who made that decision.

A complaint involving the possible failure of an IVD to meet any of its performance specifications must be reviewed, evaluated, and investigated, as required by § 820.198(b). The complainant need only indicate the possible, not confirmed, failure of an IVD.

There are several different mechanisms for receiving complaints. Replacement of a complainant's product has, in many instances, been the basis for deciding not to investigate a complaint any further. This is not an acceptable follow-up to a report of contaminated product or failure of the IVD to perform within its specifications. If the replacement was performed and it meets the definition of a complaint as defined in § 820.198(a), then the complaint must be reviewed, evaluated, and maintained by a formally designated unit; and, if the complaint involves the possible failure of an IVD to meet any of its performance specifications, then the complaint must be reviewed, evaluated, and investigated. Product credit sheets are routinely maintained by customers which list defective lots, or defective portions of lots, and these sheets are then returned to the IVD manufacturer for credit or replacement of the items. The credit or replacement sheets are reviewed by the formally designated unit to determine which credits or replacements meet the definition of a complaint as defined in § 820.198(a). All credits or replacements which meet the definition of a complaint must be reviewed, evaluated, and maintained; and, if the credit or replacement meets the definition of a complaint, and the complaint involves the possible failure of an IVD to meet any of its performance specifications, then the complaint must be reviewed, evaluated, and investigated. Also, IVD manufacturers routinely manufacture IVDs for themselves and for their own label distributors, other IVD manufacturers, or foreign subsidiaries or manufacturers. The IVD manufacturer has a feedback mechanism in place whereby complaints on their products, received by other organizations, are forwarded to the original manufacturer for review and evaluation.

The extent of a complaint investigation may involve several areas: 1) requesting that the complainant return the product to the manufacturer for examination and testing; 2) examination and testing of the same lot of IVD from the manufacturer's warehouse or reserve sample stock; and, 3) examination of the device history record for the lot to determine if manufacturing and testing procedures were accurately followed, and if all specifications were met prior to release of the IVD lot.

Once the actual failure of a product to meet specifications is identified, the failure investigation requirements of § 820.162 take effect. A written record of the investigation, including conclusions and follow-up, is required.

If the investigation finds that the lot, or lots, of the IVD do not meet specifications, appropriate corrective action must be instituted. This may include: review of processes and procedures, and making changes where necessary; review of package design and stability studies, and making changes where necessary; and, appropriate corrective action on the remainder of the IVD product in the marketplace, such as recall.

Any complaint pertaining to injury or death, or any hazard to safety, must be immediately reviewed and investigated by a designated individual, and maintained in a separate portion of the complaint file. In addition, complaints must be evaluated to determine if any meet the definition of, and reporting requirements of, medical device reporting as defined in Part 803 of the regulations.

Establishing a written complaint handling procedure is a good quality assurance practice to outline all steps involved in receiving, handling, reviewing, maintaining, and investigating complaints, so that all individuals involved in all aspects of the complaint process are operating under similar directions.

3.11 TREND ANALYSIS

In the July 1978 preamble to the GMP regulation, "statistical control" in proposed § 820.100(c), regarding ongoing trend analysis, was believed to be confusing and essentially duplicating the requirement in § 820.100(b), and was deleted. Section 820.100(b) requires written procedures describing any processing controls necessary to ensure conformance to specifications where deviations from device specifications could occur as a result of the manufacturing process itself. Section 820.20(a)(3) requires that the quality assurance program consist of procedures to identify, recommend, or provide solutions for quality assurance problems and verify the implementation of such solutions. The following are means of complying with these requirements.

Product and process accept/reject data results, along with information from complaint files collected through various documented process and control systems, are evaluated by appropriate methods (e.g., trend analysis) to determine if there are recurring problems or process drift which warrant corrective action. Trend analysis is an important part of an effective quality assurance program and is important for identifying conditions or situations such as performance problems with specific lots or products, seasonal increases in contamination, component vendor problems, or process drift, which might otherwise not be apparent or dismissed as isolated incidents. When such trends are examined, areas of concern or system/process failures may be identified. Measures can then be established and implemented to control or eliminate their reoccurrence.

APPENDIX I
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12 *Standard Test Method for Determining Bacterial Retention of Membrane Filters Utilized for Liquid Filtration*, American Society for Testing and Material (ASTM), F838-83, ASTM, Philadelphia, PA 19163.

13 *Validation Guide*, Publication TR-680, September 1980, Pall Corp.

14 *The United States Pharmacopeia (USP) and The National Formulary (NF)*, The United States Pharmacopeial Convention, Inc., Rockville, MD 20852.

15 *Guideline on Sterile Drug Products Produced by Aseptic Processing*, June 1987, Maintained by FDA, Division of Drug Quality Compliance, HFN-320, 5600 Fishers Lane, Rockville, MD 20857.

16 *Device Good Manufacturing Practices Manual*, 5th Edition, August 1991, FDA, CDRH, HFZ-220, 5600 Fishers Lane, Rockville, MD 20857.

17 *Sterile Medical Devices: A GMP Workshop Manual*, 4th Edition, January 1985, FDA, CDRH, HFZ-220, 5600 Fishers Lane, Rockville, MD 20857.

18 *Validation of Aseptic Filling for Solution Drug Products*, Technical Monograph No. 2, 1980, PDA, Philadelphia, PA 19107.

19 *Validation of Aseptic Drug Powder Filling Processes*, Technical Report No. 6, 1984, PDA, Philadelphia, PA 19107.

20 *HIMA Medical Device Sterilization Monographs: Validation of Sterilization Systems*, Report No.: 78-4.1, June 1978, Health Industries Manufacturers Association (HIMA), Washington, DC 20005.

21 *Federal Standard 209D: Clean Room and Work Station Requirements, Controlled Environment*, June 15, 1988, General Services Administration, Federal Supply Service, Washington, DC 20407.

22 D.B. Detmore & W.N. Thompson, *A Comparison of Air Sampler Efficiencies*, 3:45-48, 52, 1981, Medical Device Diagnostic Industry (MD&DI), Santa Monica, CA 90405.

23 CDC/NIH, *Biosafety in Microbiological and Biomedical Laboratories*, 1st Edition, March 1984, Centers for Disease Control and National Institutes of Health.

24 M.C. Gould, *Endotoxin Vertebrate Cell Culture*, In Vitro Monograph No. 5, page 125, Tissue Culture Association, Gaithersburg, MD 20879.

The following references are also recommended for assuring compliance with the GMP regulation.

25 *FDA Compliance Program Guidance Manual*, Compliance Program (CP) 7382.830, Inspection of Medical Device Manufacturers, October 1988, FDA.

26 *FDA Compliance Program Guidance Manual*, Compliance Program 7382.830A, Sterilization of Medical Devices, October 1988, FDA.

APPENDIX II
DEFINITIONS

Biological Safety Cabinets -	primary containment devices in which work may be performed on infectious agents.
Class 100 -	a clean room or clean zone where the measured particles per cubic foot of size are equal to or greater than any one or more of the following particle sizes: 100 particles per cubic foot of a size 0.5 micrometers and larger; 300 particles per cubic foot of a size 0.3 micrometers and larger; and, 750 particles per cubic foot of a size 0.2 micrometers and larger.
Dead Leg -	any section of pipe or other conduit, whose length is six or more times greater than its internal diameter, which is in a fluid distribution system that either carries the fluid through the system or is not drained daily.
Filtered -	IVDs which have been processed through a filter greater than 0.22 micrometer in size to remove only certain types of organisms, and their production specifications and product labeling state: 1) the final filter pore size used; 2) the specific viable microorganisms that have and have not been removed from the product by filtration; and, 3) the specific microorganisms whose presence and absence has been confirmed through testing of the finished IVD.
Media Fills -	a method of prospectively validating sterile and microbiologically controlled IVD assembly processes using a sterile growth nutrient medium to simulate product filling operations. The nutrient medium is manipulated and exposed to the operators, equipment, containers, closures, surfaces, and environmental conditions to closely simulate the same exposure which the product itself will undergo. The media filled containers are then incubated to determine contamination or whether microbial specifications are met.
Microbiological Assurance Level (MAL) -	process specification which assures that microbiologically controlled IVDs are manufactured under appropriate conditions and controls which will result in a product which consistently meets all its specifications, where the MAL is commensurate with the need for safe and effective performance of the IVD.

Microbiologically Controlled IVD -	an IVD which may contain microorganisms which have been shown through process validation not to adversely affect product performance throughout the product's expected shelf life when stored according to the IVDs' labeling.
Microbiologically Uncontrolled IVD -	an IVD which may contain that are toxic to microorganisms or do not support the growth of microorganisms, and the remains or byproducts of any microorganisms in the IVD do not adversely affect product performance.
Retentive Filters -	a filter placed in the process or product line to trap contaminants, where filter porosity may vary depending on the type of contaminants being retained.
Sterile -	the complete absence of viable microorganisms from the product, as defined in USP, Section 1211.
Sterility Assurance Level (SAL) -	the probability of an item being nonsterile, dependent on the product bioburden and the lethality of the sterilization process.
Sterile Filtered/ Sterilized by Filtration -	IVDs which have been filtered through a not greater than 0.22 micrometer or smaller filter (which has been suitably challenged as per USP) either to remove all viable microorganisms, or to remove only certain types of microorganisms, and their production specifications and product labeling state: 1) the final filter pore size used; 2) the specific viable microorganisms that have been removed from the product by filtration; and, 3) the specific microorganisms whose absence has been confirmed through testing of the finished IVD.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 88D-0087]

Manufacture of In Vitro Diagnostic Products; Current Good Manufacturing Practice Final Guideline; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a final guideline entitled "Guideline for the Manufacture of In Vitro Diagnostic Products" that contains production practices which are acceptable to FDA for assuring the safety and effectiveness of in vitro diagnostic products. Manufacturers of in vitro diagnostic products may find the information in the guideline useful in developing procedures that comply with the current good manufacturing practice (CGMP) regulations for these products. A draft document was previously made available for public comment.

DATES: Comments by March 11, 1994.

ADDRESSES: Submit written requests for single copies of the final guideline to the Division of Small Manufacturers Assistance (HFZ-220), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-6597 (toll free outside MD 800-638-2041). Send two self-addressed adhesive labels to assist that office in processing your requests. Submit written comments on the final guideline to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857. Requests and comments should be identified with the docket number found in brackets in the heading of this document. The final guideline and received comments are available for public examination in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

FOR FURTHER INFORMATION CONTACT: Z. Frank Twardochleb, Center for Devices and Radiological Health (HFZ-300), Food and Drug Administration, 2098 Gaither Rd., Rockville, MD 20850, 301-594-1128.

SUPPLEMENTARY INFORMATION: FDA first announced the availability for public comment of the draft guideline in the Federal Register of April 7, 1988 (53 FR 11561). In that same issue of the Federal Register (53 FR 11561), FDA announced the forthcoming meeting of the agency's Device Good Manufacturing Practice Advisory Committee (the committee). As a result of the notice and the open public meeting, FDA received 17 letters providing comments—14 from manufacturers, 2 from trade associations, and 1 from an attorney representing a manufacturer. Presentations before the committee by industry and FDA resulted in committee recommendations that the agency: (1) Continue to handle the document as a guideline; (2) change the title and/or scope of the document to clarify which products are subject to the guideline; and (3) extend the comment period from June 6, 1988 to July 15, 1988.

FDA extended the comment period as recommended by the committee and revised the guideline based on the comments received. A notice of availability of the second draft was published in the Federal Register of April 19, 1990 (55 FR 14863).

Since release of the second draft, four letters of comment have been received from two trade associations, one manufacturer, and one user association. Meetings have also been held with the two trade associations—the Association of Microbiological Diagnostic Manufacturers and the Health Industry Manufacturers Association. A total of 21 letters of comment were received in response to all notices. These comments are on file with the Dockets Management Branch under Docket No. 88D–0087.

The notice of availability of the draft guideline stated that it would be issued under § 10.90(b) (21 CFR 10.90(b)), which provides for the use of guidelines to establish procedures or standards of general applicability that are not legal requirements but that are acceptable to the agency. The agency is now in the process of considering whether to revise § 10.90(b). Although that decision has not been made, the agency has decided to publish this guideline. However, this notice and the final guideline are not being issued under the authority of § 10.90(b), and the final guideline, although called a guideline, does not operate to bind FDA or any other person in any way. The agency advises that this final guideline represents its current position on the requirements of the CGMP regulations for in vitro diagnostic products. The guideline may be useful to manufacturers of in vitro diagnostic products. A person may also choose to use alternate procedures even though they are not provided for in the guideline. If a person chooses to depart from the practices and procedures set forth in the final guideline, that person may wish to discuss the matter further with the agency to prevent an expenditure of money and effort on activities that may later be determined to be unacceptable by FDA. This guideline does not bind the agency, and it does not create or confer any rights, privileges, or benefits for or on any person.

On November 23, 1993 (58 FR 61952), FDA issued a notice of proposed rulemaking to revise the medical device CGMP regulations. Any revisions to the CGMP regulations may result in the need for changes to this guideline. Therefore, on issuing a final rule to revise the CGMP regulations, FDA will review the guideline and make any necessary changes.

Copies of this final guideline, along with previous drafts and submitted comments, are available for public examination in the Dockets Management Branch (address above).

Interested persons may submit written comments on the final guideline to the Dockets Management Branch. Additional comments will be considered in determining the future need for amending the final guideline. Two copies of comments should be submitted, except that individuals may submit one copy. Comments should be identified with the docket number found in brackets in the heading of this document.

Dated: January 4, 1994.

Michael R. Taylor,

Deputy Commissioner for Policy.

[FR Doc. 94–466 Filed 1–7–94; 8:45 am]

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