DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 210 and 211

[Docket No. 95N–0362]

RIN 0910–AA45

Current Good Manufacturing Practice; Proposed Amendment of Certain Requirements for Finished Pharmaceuticals

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend certain requirements of the current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. These amendments would clarify certain manufacturing, quality control, and documentation requirements and would ensure that the regulations more accurately encompass CGMP. In addition, the agency is updating the requirements for process and methods validation to incorporate guidance previously issued to industry and to reflect current practice. These proposed amendments are intended to enhance the integrity of the drug manufacturing process and the safety of drug products.

DATES: Submit written comments on the proposed rule by August 1, 1996. Submit written comments on the information collection requirements by June 3, 1996. FDA proposes that any final rule that may issue based upon this proposal become effective 90 days after its date of publication in the Federal Register.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857. Submit written comments on the information collection requirements to the Office of Information and Regulatory Affairs, OMB, New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington, DC 20503.

FOR FURTHER INFORMATION CONTACT:

Thomas C. Kuchenberg, Center for Drug Evaluation and Research (HFD–7), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301–594–1046; or

John M. Dietrick, Center for Drug Evaluation and Research (HFD–325), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301–594–0098; or

William G. Marnane, Center for Veterinary Medicine (HFV–143), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301–594–0678; or

Nancy Roscioli, Center for Biologics Evaluation and Research (HFM–205), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448, 301–827–3031.

To obtain a copy of this document, contact the Division of Congressional and Public Affairs (HFM–44), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448. Send one self-addressed adhesive label to assist that office in processing your requests.

The document may also be obtained by mail or FAX by calling the Center for Biologics Evaluation and Research Voice Information System at 1–800–835–4709.

Persons with access to the INTERNET may obtain the document in several ways.

Users of ''Web Browser'' software, may obtain this document via the World Wide Web by using the following Uniform Resource Locators (URL's): http://www.fda.gov/cber/cberftp.html or ftp://ftp.fda.gov/CBER/

The document may also be obtained via File Transfer Protocol (FTP). Requesters should connect to the FDA FTP Server, FTP.FDA.GOV(192.73.61.21). The Center for Biologics Evaluation and Research (CBER) documents are maintained in a subdirectory called ''CBER'' on the server. Logins with the user name of anonymous are permitted, and the user's e-mail address should be sent as the password.

The ''READ.ME'' file in that subdirectory describes the available documents which may be available as an ASCII text file (*.TXT), or a WordPerfect 5.1 or 6.x document (*.w51,wp6), or both.

Finally, the document can be obtained by ''bounce-back e-mail''. A message should be sent to: ''CGMP@a1.cber.fda.gov''.

SUPPLEMENTARY INFORMATION:

I. History of the CGMP Regulations

On October 10, 1962, Congress enacted the Drug Amendments of 1962 (Pub. L. 87–781). The amendments include section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 351(a)(2)(B)), which deems a drug to be adulterated if:

> * * * the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.

In the Federal Register of June 20, 1963 (28 FR 6385), FDA published the first CGMP regulations (now codified as 21 CFR parts 210 through 226).

FDA has amended these regulations several times since 1963 to ensure that they reflect the level of control necessary and that they incorporate current technology to the extent that it influences compliance with CGMP. Major revisions of the CGMP regulations were issued in the Federal Registers of January 15, 1971 (36 FR 601), September 29, 1978 (43 FR 45014), and January 20, 1995 (60 FR 4087). The latter revision came about as the result of a comprehensive assessment of the CGMP regulations, pursuant to the Regulatory Flexibility Act (Pub. L. 96–354). During the assessment, the agency solicited comments from the public with respect to any regulations that might be perceived as being unnecessarily costly, burdensome, or lacking public benefit. The revisions that became final in January 1995 were based on the comments that FDA received as well as the agency's experience in applying those regulations.

II. Background of the Regulations

Since the development of the CGMP regulations, FDA has balanced the need for precise, easily understood standards, which ease both compliance and enforcement burdens, with the need to encourage innovation and the development of improved manufacturing technologies. The agency continues to balance such issues as part of the regulatory process, and to choose the means of regulation most suited to any particular aspect of the manufacturing process. The agency strives to provide manufacturers with the discretion on how to achieve the level of control necessary under CGMP, recognizing that in a few instances, more direction from the agency is necessary because of the potential for harm, the narrow range of acceptable means to accomplish a particular CGMP objective, or to provide a uniform standard to the entire industry. The CGMP regulations are based on fundamental concepts of quality assurance: (1) Quality, safety, and effectiveness must be designed and built

into a product; (2) quality cannot be inspected or tested into a finished product; and (3) each step of the manufacturing process must be controlled to maximize the likelihood that the finished product will be acceptable (Ref. 1).

To accomplish these objectives, the agency must periodically reassess and revise the CGMP regulations to accommodate advances in technology that further safeguard the drug manufacturing process. As technology and scientific knowledge evolve, so does understanding of the critical material, equipment, and process variables that must be defined and controlled to ensure end product homogeneity and conformity with appropriate specifications. The CGMP regulations would not achieve their statutorily mandated purposes if they were not periodically reassessed to identify and eliminate obsolete provisions or to modify provisions that no longer reflect the level of quality control that current technology dictates and that the majority of manufacturers have adopted.

Despite the agency's historic preference for a general regulatory approach in the CGMP regulations, experience has shown that additional specificity is warranted in certain areas. In addition, FDA regulatory activities, and particularly its enforcement activities, have demonstrated a need for greater uniformity in certain procedures to protect the integrity of the drug product. When experience has demonstrated that the acceptable choices with respect to any given regulation are limited, FDA believes that the regulations will better serve the public by reflecting the actual processes and procedures that are acceptable to FDA. In those relatively few instances where such specificity has been introduced into the regulations, FDA believes industry will benefit by being able to focus its resources on activities and processes that are known to be appropriate, rather than on those that may eventually be found to be deficient.

FDA has determined that revisions to the CGMP regulations are necessary at this time for a number of reasons. Rapid changes in technology have created situations not anticipated when the CGMP regulations were originally written or last revised. The agency's enforcement and litigation experience has revealed persistent lack of understanding among a limited number of manufacturers with respect to certain of the CGMP regulations. Some pharmaceutical firms have not subjected their procedures to sufficient scrutiny, while others have failed to update such procedures to accommodate changes or advances in the manufacturing process. In some cases, manufacturers may be relying on methods and procedures that were acceptable at some time in the past, but that are not acceptable in light of current standards.

In addition, FDA investigators have encountered serious validation deficiencies at a number of firms. FDA is particularly concerned with validation procedures designed to ensure the quality of the manufacturing process. Enforcement and compliance actions have also revealed a need for greater clarity and specificity in some portions of the regulations.

These proposed revisions would, therefore, amend certain requirements, define or redefine certain terms, and clarify industry obligations with respect to several portions of the regulations. In addition, the agency is proposing to revise certain laboratory control and cross-contamination requirements and to clarify proper testing procedures.

FDA believes that the procedures that would be required by this proposal reflect practices already used by many manufacturers and represent the prevailing industry standard. The agency emphasizes, however, that for a given practice to be considered a current good manufacturing practice (or promulgated as such in the regulations), it is not a prerequisite that the practice actually be in use by a majority, or a specific percentage of, the industry.

FDA has endeavored to ensure that the drug manufacturing process will consistently produce products that are safe and have the quality and purity which they purport to have, while recognizing the interests of firms in retaining some discretion in achieving the level of control necessary to comply with CGMP. FDA believes that the proposed rule successfully addresses this balance; however, FDA invites comments addressing specific proposals.

Other organizations have developed standards to define quality in the manufacturing process. One such organization is the International Organization of Standardization (ISO). The purpose of the ISO 9000 Standards is to provide generic guidance on quality in manufacturing processes to both industry and vendors supplying industry. Five standards (9000–9004) have been developed by the ISO Council and are intended to be accepted worldwide. These standards are applicable to any industry and are not specific to the pharmaceutical industry. Compliance with the standards is voluntary. The principles and practices elucidated in the ISO standards are not in conflict with those provided by the CGMP regulations. Indeed, the voluntary ISO standards share common principles with FDA's CGMP requirements.

III. Highlights of the Proposed Rule

The proposed rule would amend or revise a number of CGMP provisions as follows:

A. Process Validation

The proposed rule would define ''process validation.'' Process validation is a quality assurance function that helps to ensure drug product quality by providing documented evidence that the manufacturing process consistently does what it purports to do. Although process validation is widely practiced by industry, FDA continues to find firms that have never validated manufacturing processes for some finished products.

Manufacturing process validation is a continuous undertaking through which the process performance is constantly monitored and evaluated. The complexities of modern manufacturing processes may make it necessary to adapt or alter existing parameters while unexpected variables may affect the manufacturing process and the finished product. For example, a slight change in the physical characteristics of an ingredient, or in the order of adding ingredients, may alter the bioavailability of a drug product. In such a case, a sample of the finished product could meet compendial dissolution criteria but present a substantially different dissolution pattern than that produced before changes were made. Because of such effects, revalidation may be necessary after any change in process or product characteristics or control procedures.

Although FDA has found numerous instances in which some firms have failed to revalidate their processes for many years, the agency recognizes that most of industry establishes and follows process validation standards. Moreover, most in industry recognize the need for revalidation (Ref. 2):

> To preserve the validated status of a process, measures must be taken that will allow any significant process changes to be recognized and addressed promptly. Such change control measures can apply to equipment, standard operating procedures, manufacturing instructions, environmental conditions, or any other aspect of the process system that has an effect on its state of control, and therefore on the state of validation.

Accordingly, the agency is proposing to add new § 211.220 to the CGMP regulations specifying the nature and extent of validation that are necessary to

ensure that the resulting products have the identity, strength, quality, and purity characteristics that they purport to possess. The proposed regulation also clarifies this requirement by using the term ''validation'' for those elements of the manufacturing process under the control of the manufacturer, while the term ''verification'' is used for those items produced by a person other than the manufacturer or otherwise not under the control of the manufacturer.

FDA believes that the proposed rule reflects current industry standards and processes that are implemented by many in the industry. The proposed rule is necessary to: (1) Clarify the requirement to those firms that have not implemented or properly conducted validation; (2) ensure that all manufacturers are applying, and are evaluated against, the same standard; and (3) clarify any remaining confusion about the importance of validation in CGMP. FDA invites comments on whether this proposal adequately achieves these goals in a manner consistent with current industry practice.

B. Methods Validation

This proposed rule would also define in § 210.3 ''methods validation,'' which is the documented, successful evaluation of an analytical method that provides a high level of assurance that such method will consistently yield results that are accurate within previously established specifications. The agency is proposing to move the requirement for methods validation from § 211.165(e) to § 211.222 for emphasis and to change the word ''established'' to ''validated'' for clarification. Current regulations require regulated firms to validate all analytical methods that vary from compendial methods. The suitability of a chosen method may be measured by such analytical variables as precision, accuracy, limit of detection, limit of quantitation, selectivity, range, linearity, and ruggedness. Methods validation is intended to provide a high level of confidence that the method selected is scientifically sound and that it serves its intended analytical purpose.

Methods validation is central to ensuring the reliability of all evidence that supports a product's identity, strength, quality, and purity. For test results to be useful, significant, and reliable, the methods used to analyze the data in such test results must also be validated. In other words, a firm must establish that the analytical methods it uses to assess or evaluate a manufacturing process accurately measure variables affecting process control.

FDA recognizes that the scientific soundness of most of the methods used by firms is well established. Compendial methods, for example, reflect years of experience and evaluation and, in most cases, do not need to be revalidated. In some instances, however, no generally recognized analytical method exists or problems may develop with existing methods. Product modification may also lead to innovative analytical methods. FDA inspections have revealed that some firms use methods that have become outdated, or claim to use analytical methods that bear little relationship to those actually being used. In such cases, new or revised analytical methods must be established as scientifically sound and reproducible. FDA invites comments on this proposal with respect to alternative means, if any, of assuring the reliability of analytical methods.

C. Contamination

Drug products can become contaminated in a variety of ways. For example, ineffective cleaning procedures may leave residues of the product or cleaning agents in the equipment, production workers may fail to take proper precautions while transporting a substance from one area to another thereby introducing a contaminant to the second production area, or particles may become airborne and travel to production areas throughout the facility. Drug products may become contaminated by a number of substances such as dust, dirt, debris, toxic substances, infectious agents, or residue of other drugs or drug components. Most contamination can be controlled to an acceptable level through measures such as proper planning and implementation of cleaning processes, employee training, gowning, and air filtration. Under CGMP, a manufacturer will set contamination limits on a substance-by-substance basis, according to both the potency of the substance and the overall level of sensitivity to that substance.

However, controlling or reducing the likelihood of contamination is inadequate when substances are present that may pose a serious risk to humans or animals because their presence in even trace amounts may render toxic an otherwise safe product. This is of particular concern because a toxic reaction resulting from cross-contamination may not be apparent to a health professional treating a patient suffering from such a reaction, or may be impossible to trace to product contamination. Penicillin, for example, is a substance that poses an unacceptable risk of contamination because of the severe reaction some humans have to it even at very low levels of exposure. Penicillin has long been subject to specific CGMP regulations designed to reduce the danger of cross-contamination. Because other substances, such as cytotoxic agents or other antibiotics, pose at least as great a risk of toxicity due to cross-contamination, FDA is proposing to expand the contamination control requirements to encompass other sources of contamination.

FDA has determined that substances posing a serious threat of contamination, i.e., substances to which humans or animals show a particular sensitivity even at extremely low levels, should be controlled through dedicated production processes. For example, dedicated facilities, air-handling equipment, and process equipment may be necessary. The agency has refrained from establishing a list of drugs or drug products that present such an unacceptable risk, because such a list would quickly become obsolete. Moreover, the agency believes that most manufacturers are knowledgeable about risks that are associated with products that they produce, as well as with the effective means to prevent cross-contamination. FDA stresses that prevention of cross-contamination of potentially toxic substances is the goal of this proposed rule. Because, in even small amounts, those drugs may be toxic to humans or animals, FDA expects manufacturers to identify any drugs that they produce that present the risk of cross-contamination and to implement measures necessary to eliminate that risk. FDA recognizes that, depending on the drug product, a variety of measures may be acceptable to eliminate cross-contamination; there may, however, be situations in which nothing short of dedicated facilities or equipment will be sufficient. FDA invites comments on this proposal especially with respect to any alternative means of addressing and preventing cross-contamination.

D. Testing

FDA has concluded through its inspection and enforcement activities that many manufacturers are not conducting adequate testing procedures and are not adequately evaluating test discrepancies or investigating failures. Such an investigation is crucial to ensure that the manufacturing process is adequately controlled.

FDA recognizes the need to clarify the CGMP requirements in this area so that all manufacturers are applying the same

minimum standards and so that all manufacturers are thoroughly assessing test results and discrepancies to ensure that all drug products are safe and of the quality and purity which they purport to be. This proposed rule would amend procedures for the testing of components, calculation of yield, and blend testing. It would also provide procedures for dealing with out-of-specification results. FDA invites comments on alternate means of achieving adequate followup of testing discrepancies or failures.

E. Quality Control

To further ensure that validation procedures are current, this proposed rule would make the quality control unit responsible for reviewing changes in product, process, equipment, or personnel, and for determining if and when revalidation is required. The agency believes that placing responsibility for oversight of validation procedures in quality control units emphasizes the importance of proper validation to quality control. This proposed rule stresses the importance of validation by ensuring that a manufacturer will have a certain employee or employees who are responsible for and accountable for ensuring that the firm adequately evaluates its manufacturing process, validates the processes and testing that must be validated, and thoroughly assesses any discrepancies. FDA believes that this proposed regulation will enhance compliance with CGMP through a means acceptable to most manufacturers while providing FDA the ability to ensure accountability and compliance.

IV. Description of the Proposed Rule

In general, the proposed rule would add new definitions to § 210.3 to clarify existing terms in the CGMP regulations and to reflect proposed changes to the CGMP regulations for finished pharmaceuticals. This proposal would also revise the CGMP regulations for finished pharmaceuticals in part 211 to incorporate validation, test, and documentation procedures necessary to protect the integrity of the drug manufacturing process. Specific provisions are described in more detail below.

A. Section 210.3—Definitions

Current § 210.3(b) defines various terms that are used in the CGMP regulations in parts 210 to 226.

This proposed rule would amend § 210.3(b) to include new definitions to clarify existing terminology and to define new terms introduced in other provisions of this proposal. Under proposed § 210.3(b)(23), ''validation protocol'' would mean a written plan describing the process to be validated, including production equipment and how validation will be conducted. Such a plan would address objective test parameters, product and process characteristics, predetermined specifications, and factors which will determine acceptable results.

Proposed § 210.3(b)(24) would define ''process validation'' as establishing, through documented evidence, a high degree of assurance that a specific process will consistently produce a product that meets its predetermined specifications and quality characteristics.

This proposal would define ''methods validation'' in § 210.3(b)(25) as establishing, through documented evidence, a high degree of assurance that an analytical method will consistently yield results that accurately reflect the quality characteristics of the product tested.

Proposed § 210.3(b)(26) would define ''equipment suitability'' as the established capacity of process equipment and ancillary systems to operate consistently within established limits and tolerances.

Under proposed § 210.3(b)(27), ''process suitability'' would mean the established capacity of the manufacturing process to produce effective and reproducible results consistently.

Proposed § 210.3(b)(28) would define ''out-of-specification'' as an examination, measurement, or test result that does not comply with preestablished criteria. This definition would be consistent with § 211.160(b), which requires laboratory controls for finished pharmaceuticals to include the establishment of scientifically sound and applicable specifications, standards, sampling plans, and test procedures designed to ensure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity.

Proposed § 210.3(b)(29) would define ''reprocessing'' as a system of reworking batches that do not conform to standards or specifications, including ''the steps taken to ensure that the reprocessed batches will conform to all established standards, specifications, and characteristics.'' Under the proposal, ''reprocessing'' would include a step or steps in the manufacturing process that are out of the normal processing sequence or that are not specifically provided for in the process.

Under proposed § 210.3(b)(30), ''manufacturing process'' would mean all manufacturing and storage steps in the creation of the finished product from the weighing of components through the storing, packaging, and labeling of the finished product, including, but not limited to, the following: Mixing, granulating, milling, molding, formulating, lyophilizing, tableting, encapsulating, coating, sterilizing, and filling.

B. Section 211.22—Responsibilities of Quality Control Unit

Current § 211.22 describes a quality control unit's responsibilities. These responsibilities include ''the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products'' as well as the authority to review production records to determine whether errors have occurred. If errors have occurred, § 211.22 also gives quality control units the authority to determine whether a firm has fully investigated the error.

The agency understands that some manufacturers would prefer that the term ''quality control'' be replaced with ''quality assurance,'' that the functions of quality control and quality assurance be somehow differentiated, or that a number of other terms be incorporated into the regulation to reflect the distribution of quality oversight responsibilities in various manufacturing settings.

FDA does not believe that such changes in terminology would be useful. The difference between ''quality assurance'' and ''quality control'' is recognized to be operational. The quality control unit is usually responsible for performing the testing to assure that proper specifications and limits are adhered to, while the quality assurance unit is responsible for auditing methods, results, systems, and processes, and for performing trend analyses. The functions described in the proposed rule as the responsibility of the quality control unit are designed to be implemented by all manufacturers, regardless of size or organizational structure. However, such procedures can easily be accommodated under organizational structures which utilize quality assurance and quality control departments. The agency stated in the preamble to the 1978 CGMP regulation and reiterates here, that the term quality control ''unit'' is used in the regulations ''because it is a term broadly applicable to any group within a manufacturing establishment charged with the responsibility of quality control. The

Commissioner is not concerned about the name given by a firm to its own unit that is responsible for quality control functions'' (43 FR 45014 at 45032).

Proposed 211.22(a) would require that firms be accountable with respect to validation provisions and would give quality control units the additional responsibility of reviewing and approving validation protocols to assess their adequacy. Quality control units would also be responsible for reviewing product, process, equipment, or other changes to determine if and when revalidation is warranted. This change is intended to make the quality control unit responsible for keeping validation current and is a logical extension of the quality control unit's role in ensuring product quality. The agency believes that, by making clear such accountability, compliance with the validation provisions will be more consistent and reliable.

C. Section 211.68—Automatic, Mechanical, and Electronic Equipment

Current § 211.68(b) requires appropriate controls over computer or related systems to ensure that only authorized personnel make changes in master production and control records or other records. The current regulation also requires that ''A backup file of data entered into the computer or related system shall be maintained except where certain data, such as calculations performed in connection with laboratory analysis, are eliminated by computerization or other automated processes.'' If computerization or other automated process has eliminated such calculations, ''a written record of the program shall be maintained along with appropriate validation data.''

Proposed § 211.68(b) would replace the phrase ''appropriate validation data'' with ''data establishing proper performance.'' This change is intended to emphasize that the manufacturer must actually establish proper performance.

D. Section 211.82—Receipt and Storage of Untested Components, Drug Product Containers, and Closures

Section 211.82 governs the receipt and storage of untested components, drug product containers, and closures. Section 211.82(b) currently states, in part, that, ''Components, drug product containers, and closures shall be stored under quarantine until they have been tested or examined, as appropriate, and released.'' This provision is designed to prevent the premature release of untested components, containers, and closures that might be unsuitable for use in the manufacturing process.

The proposal would remove the words, ''as appropriate,'' to eliminate any ambiguity in the existing regulation. Although testing or examination may vary with the particular component, drug product container, or closure, the revision would also emphasize that it is, in fact, accepted industry practice to conduct some testing or examination before the components, drug product containers, or closures are released from quarantine.

E. Section 211.84—Testing and Approval or Rejection of Components, Drug Product Containers, and Closures

Section 211.84 pertains to the testing and approval or rejection of components, drug product containers, and closures. Under current § 211.84(c)(1), containers of components ''shall be cleaned where necessary, by appropriate means.''

This proposed rule would replace the phrases ''where necessary'' and ''by appropriate means'' with ''in a manner to prevent introduction of contaminants into the raw material.'' This change will clarify that the act of cleaning component containers is done for a particular purpose, to prevent the introduction of contaminants, and that purpose must, in all cases, be achieved.

FDA proposes to correct a typographical error in the text of § 211.84(c)(5) which requires that sample containers be identified so that, among other things, the date on which the sample was taken can be determined. The current regulation erroneously states ''the data on which the sample was taken.'' FDA proposes to correct this by changing ''data'' to ''date.'' Additionally, proposed § 211.84(d)(3) would make two editorial changes by replacing the word ''conformance'' with ''conformity'' and ''procedure'' with ''specifications.''

F. Section 211.101—Charge-In of Components

Current § 211.101 requires written production and control procedures to assure that drug products have the identity, strength, quality, and purity they purport or are represented to possess. Section 211.101(c) requires that weighing, measuring, or subdividing operations be adequately supervised and that each container of component dispensed to manufacturing be examined by a second person to ensure that: (1) The component was released by the quality control unit; (2) the weight or measure, as stated in batch production records, is correct; and (3) the containers are properly identified.

The proposed rule would add a fourth requirement (§ 211.101(c)(4)) that drug ingredients conform to the quality specifications for the intended drug product. Active and inactive ingredients come in varying grades and may not be interchangeable. This proposal would require examination of the component by competent and responsible individuals to ensure that the correct material is used. This provision would provide additional assurance that the raw materials used are appropriate for the intended batch, but is not intended to require testing in addition to that required under subpart E of part 211.

G. Section 211.103—Calculation of Yield

Section 211.100 currently requires maintenance of written procedures for production and process controls to ensure that drug products have the identity, strength, quality, and purity they purport or are represented to possess. Section 211.103 currently requires that actual yields and percentages of theoretical yield be determined at the conclusion of appropriate phases of manufacturing, processing, packaging, or holding of the drug product. These calculations are performed by one person and independently verified by a second person. Section 211.192 currently requires any unexplained discrepancy (including a percentage of theoretical yield exceeding the maximum or minimum percentages established in master production and control records) to be thoroughly investigated.

This proposed rule would amend § 211.103 to make clear that there must be a written production and control procedure that will require an investigation of any significant unexplained discrepancies between actual yields and percentages of theoretical yield of the drug product. This provision would help ensure that the source of any potential problem is quickly and accurately identified and addressed.

H. Section 211.110—Sampling and Testing of In-Process Materials and Drug Products

Current § 211.110 establishes several requirements for the sampling and testing of in-process materials and drug products. For example, § 211.110(a) requires written procedures for in-process controls and tests or examinations to be conducted on appropriate samples of in-process materials of each batch, whereas § 211.110(b) states that valid in-process specifications shall be consistent with drug product final specifications and shall be derived from previous acceptable process average and process

variability estimates where possible and determined by the application of suitable statistical procedures. The regulation is designed to protect the integrity of the manufacturing process and thus the safety and efficacy of the drug product.

Sampling and testing techniques, however, are valid only insofar as they provide a realistic representation of the material being sampled or tested. Blend testing is important because it increases the likelihood of quickly detecting uniformity problems that may produce inferior batches. A large sample can mask differences that may be significant in individual dosage units. Therefore, sample size must approximate dosage size to provide an accurate representation of blend uniformity. This proposal would create new § 211.110(d) to help ensure adequate testing. (The current paragraph (d) would be redesignated as paragraph (e).) Proposed § 211.110(d) would also require that sampling be demonstrated through validation to be representative of all portions of the blend.

This proposal would also require in new § 211.110(f) that validation of manufacturing processes be conducted in accordance with process validation requirements in proposed § 211.220. Validation of these processes is intended, among other things, to ensure that the sample is representative of all portions of the blend. For example, firms sampling from drums containing the finished blend must demonstrate that their sampling technique produces samples representative of the entire batch.

I. Section 211.111—Time Limitations on Production

To assure the quality of the drug product, § 211.111 currently requires, when appropriate, time limits for the completion of each phase of production.

This proposed rule would revise § 211.111 to require for time-sensitive procedures that manufacturers establish and validate maximum time for completion of such procedures as part of the validation required under § 211.220. FDA expects that the validation of time-sensitive procedures will be part of process validation.

J. Section 211.113—Control of Microbiological Contamination

Section 211.113(b) requires the establishment of, and adherence to, written procedures designed to prevent microbiological contamination of drug products purporting to be sterile. The provision also requires that such procedures include ''validation of any sterilization process.''

This proposed rule would amend § 211.113(b) to refer to validation of ''any sterilization or aseptic process.'' This change is intended to reflect the fact that whether pharmaceutical firms use aseptic processing techniques or whether they use terminal sterilization, either technique must be validated.

K. Section 211.160—General Requirements

Currently, § 211.160(b) requires that laboratory controls include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to ensure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity.

This proposal would specify a requirement for the establishment of scientifically sound resampling, retesting, and data interpretation procedures.

Currently under § 211.160(b)(1), laboratory controls shall include a determination of conformance to appropriate written specifications for the acceptance of each lot within each shipment of components, drug product containers, closures, and labeling used in the manufacture, processing, packing, or holding of drug products.

This proposal would make editorial changes, replacing ''conformance'' with ''conformity'' and ''appropriate'' with ''applicable.''

L. Section 211.165—Testing and Release for Distribution

Section 211.165(e) requires that the accuracy, sensitivity, specificity, and reproducibility of test methods used by a firm be established and documented. Because other revisions in this proposal would clarify and set forth this requirement, the proposal would remove § 211.165(e) and redesignate paragraph (f) as paragraph (e).

M. Section 211.166—Stability Testing

Currently, § 211.166 requires a written stability testing program and provides the elements of such a program. The current provision requires that an adequate number of batches be tested to determine an appropriate expiration date. This proposal would redesignate current § 211.166(c) and (d) as § 211.166(d) and (e), and add new § 211.166(c) to require placing at least one additional batch into the stability testing program each year.

For some time, requirements for new drug and abbreviated new drug applications and biological products applications have included as a condition for approval a commitment to place the initial three production batches and at least one additional batch annually into the stability testing program. It is necessary to place the three initial batches in the stability testing program to account for batch variability and to confirm the previously established expiration date.

There are, however, variations in the production process during the lifetime of a drug product such as changes in personnel, raw materials and suppliers, manufacturing environment, and equipment. Because a dosage form is typically a complex unit, such changes may have an impact on drug product stability. Because of this, the agency believes it is imperative that ongoing production be periodically monitored to ensure the stability of the product. The agency believes, further, that the necessity for continued stability testing is recognized by the industry and is now standard industry practice. The agency invites comments on this proposed provision.

N. Section 211.180—General Requirements

Section 211.180(a) requires the retention of production, control, or distribution records specifically associated with a batch of a drug product, for at least 1 year after the expiration date of the batch. FDA believes that validation records, including the validation protocol, production and control records, data, and the study report, should not be discarded after the validation batches expire. They should be retained for as long as the validated process is used and as long as any batches made by the validated process may be available to consumers. The proposal would therefore amend this section to add a requirement that the validation records required by proposed new § 211.220 also be retained for at least 1 year after the expiration date of all batches associated with that validated process.

O. Section 211.192—Production Record Review

FDA's experience has revealed a variety of written and unwritten practices and procedures under which firms have disregarded out-of-specification laboratory results, after minimal retesting, resampling, inappropriate averaging of results, or inappropriate outlier testing. Some firms then proceeded to release a product without a thorough investigation or an adequate justification for disregarding an out-of-specification result.

Out-of-specification results can be caused by laboratory error, nonprocess or operator error, or by process-related error. The agency recognizes that laboratory errors occur and that a thorough investigation, supported by evidence and documentation, may, for instance, indicate an out-of-specification result caused by laboratory personnel errors or equipment failures. However, unless and until an investigation indicates that this is the case and the investigation is completed and documented, FDA believes that the out-of-specification result should not be discarded or disregarded. Moreover, FDA emphasizes that, although retesting may be an appropriate part of an investigation, an investigation consisting solely of repeated retesting is clearly inadequate. If quality is not built into a drug product, retesting cannot make it conform to specifications.

FDA recognizes the distinction between the limited investigation that may be necessary to identify a laboratory error and the more extensive investigation and testing necessary when out-of-specification results may be attributed to another cause. The agency also recognizes that the industry may impose additional criteria beyond those required to ensure identity, strength, quality, and purity under CGMP regulations or as required by a drug application. The agency encourages such internal controls. Under such circumstances, a manufacturer could have test results that violate internal standards although they would not be out-of-specification, as defined in these regulations.

FDA believes, however, that CGMP requires written procedures to be in place to determine the cause of any apparent failure, discrepancy, or out-of-specification result. If the out-of-specification result cannot be clearly attributed to laboratory error, then the quality control unit should ensure that a thorough investigation is conducted and supported by a written record. Certain elements and procedures are crucial to a systematic and orderly investigation. Consequently, this proposed rule would revise the section heading of § 211.192 to read ''Production, control, and laboratory record review and investigation of discrepancies,'' and would amend § 211.192(b) to require written procedures including the following: (1) Procedures for attempting to identify the cause of the failure or discrepancy; (2) criteria for determining whether out-of-specification results were caused by sampling or laboratory error; (3) scientifically sound procedures and criteria for the exclusion of any test data found to be invalid due to laboratory or sampling error; (4) scientifically sound procedures and criteria for additional sampling and testing, if necessary, during the investigation; (5) procedures and criteria for extending the investigation to other batches or other products; (6) procedures for review and evaluation of the investigation, including all test results, by the quality control unit, to ensure a thorough investigation; and (7) criteria for final approval or rejection of the batch involved, and for taking action on other batches and products if indicated by the investigation.

The number of retests performed before a firm concludes that an unexplained out-of-specification laboratory result is invalid, or that a product is unacceptable, is a matter of scientific judgment. FDA does not intend to issue regulations on specific retesting procedures. Rather, the proposed rule would require each firm to have written investigation and retesting procedures, applying scientifically sound criteria, that limit the amount of retesting permitted and indicate the point at which testing ends and the product is evaluated.

Proposed § 211.192(c) would require written records of the investigation to be made and shall include: (1) The reason for the investigation; (2) a description of the investigation made, including all laboratory tests; (3) the results of the investigation including all laboratory test results involved in the investigation; (4) scientifically sound and appropriate justification for excluding any out-of-specification laboratory result found to be invalid; (5) if laboratory results are found to be invalid, the subsequent laboratory results supporting the final determination of the tested item's conformity to appropriate specifications for acceptance; (6) the conclusions and subsequent actions concerning all batches and products that may have been associated with the failure or discrepancy; (7) the signature(s) and date(s) of the person(s) responsible for approving the record of the investigation; and (8) the signature(s) and date(s) of the person(s) responsible for the final decision on disposition of the batch, and on other batches and products involved. The agency specifically invites comments on these proposed requirements.

P. Section 211.220—Process Validation, and Section 211.222—Methods Validation

FDA proposes to add new subpart L to part 211 entitled ''Validation.'' The new subpart would consist of two regulations: § 211.220 for ''process validation'' (establishing through documented evidence a high degree of assurance that a specific process will consistently produce a product that meets predetermined specifications and quality characteristics), and § 211.222 for ''methods validation'' (establishing through documented evidence a high degree of assurance that an analytical method will consistently yield results that accurately reflect the quality characteristics of the material tested).

These proposed regulations are intended to clarify the requirements for validation and to provide the basic elements of an acceptable validation procedure. FDA believes, in general, that scientific knowledge and industry experience have defined the basic elements of a sound validation system. Validation has proven to be an effective technique for protecting the integrity of the drug manufacturing process.

Although the particular requirements of process validation will vary according to such factors as the nature of the drug product (e.g., sterile versus nonsterile) and the complexity of the process, the requirements of the proposed subpart are generally applicable to all drug products and provide a foundation for building a comprehensive approach to process validation.

Proposed § 211.220(a) would require validation of all drug manufacturing processes including, but not limited to, computerized systems involved in the manufacturing process. Under the proposal, the manufacturing process would include all manufacturing steps in the creation of the finished product, including, but not limited to, cleaning, weighing, measuring, mixing, blending, compressing, filling, packaging, and labeling. Time-sensitive steps in the manufacturing process would be validated. Such validation ensures that the impact of any interruption in the manufacturing process on drug product safety and efficacy is fully understood by the manufacturer.

Proposed § 211.220(b) would establish requirements for a validation protocol. The validation protocol is the blueprint of the validation process for a particular drug product. The protocol would specify a sufficient number of replicate process runs to demonstrate reproducibility and provide an accurate measure of variability among successive runs. Validation documentation would include evidence of the suitability of materials and the proper performance and reliability of the equipment and systems used to manufacture a drug product. The execution of the protocol and the test results would be

documented and the manufacturer would be required to retain such documentation.

Proposed § 211.220 would require that equipment and processes be designed and selected to be consistently capable of achieving product specifications. Determining equipment suitability would include testing to verify whether the equipment is capable of performing adequately within the operating limits of the process. A determination of process suitability would include rigorous testing and documentation to demonstrate that the process is both effective and reproducible. A manufacturer should test those parts of the process that may affect product quality or may cause variability.

Proposed § 211.220(d) would require a quality assurance system to implement revalidation procedures whenever there are changes, including reprocessing, that could affect product effectiveness or product characteristics, or whenever changes are observed in product characteristics.

Proposed § 211.222, ''methods validation,'' would require the manufacturer to establish and document the accuracy, sensitivity, specificity, reproducibility, and any other attribute necessary to validate test methods. The validation would be required to meet the existing requirements for laboratory records provided at § 211.194(a)(2). These requirements include a ''statement of each method used in the testing of the sample,'' indicating the location of the data that establish that the methods used in testing the sample meet proper standards of accuracy and reliability as applied to the tested product. The proposed provision is designed to ensure that testing methods used are relevant to product quality and the integrity of the manufacturing process. FDA invites comments on this proposal, especially on alternative means, if any, of assuring the reliability of manufacturing processes and analytical methods.

Q. Section 211.240—Control of Chemical and Physical Contaminants

FDA's experience indicates that the potential dangers of contamination are more extensive and varied than once believed; for example, high potency drugs, such as penicillin, cephalosporins, and cytotoxic anticancer agents, may pose health risks even at low levels of exposure. Cross-contamination may result in the adulteration of other drugs, and even minimal amounts could have serious adverse effects on persons who are allergic to the contaminant. Moreover, because the identity or even the presence of the contaminant may be unknown, health care professionals providing care to a patient suffering from such an adverse effect may be unable to provide appropriate medical intervention.

FDA is thus proposing to add new subpart M, which would be directed to the control of chemical and physical contaminants. The new subpart, consisting of proposed § 211.240, would require firms to anticipate and prevent specific contamination problems, including, but not limited to, those presented by penicillin. As a result, FDA is also proposing to remove §§ 211.42(d) and 211.176 regarding separate facilities for manufacturing penicillin and penicillin contamination and to incorporate their requirements in § 211.240.

Proposed § 211.240(a) would require the implementation of written procedures designed to prevent objectionable chemical and physical contamination, including cross-contamination. Section 211.240(b) would require dedicated production, which may include facilities, air handling, or process equipment, in those circumstances in which contaminants pose a special danger to human or animal health. Such contaminants include, but are not limited to, penicillin, cephalosporins, cytotoxic anti-cancer agents, and infectious agents (e.g., spore-bearing organisms and live viruses). Dedicated production would also be required under proposed § 211.240(b) if there are no reasonable methods for the cleaning and removal of a drug substance or compound residues from buildings, facilities, and equipment.

If there is a reasonable possibility that a drug has been exposed to cross-contamination, proposed § 211.240(c) would require that the product be tested for the potential contaminant. It would also require the establishment of limits for potential contaminants, and prohibit the release of a product for distribution if these limits are exceeded.

The proposed contamination provisions are designed to accommodate technological changes. For example, under the proposed rule, a manufacturer might develop a drug product of high therapeutic potential that also poses a high risk of contamination. If this hypothetical drug product contamination posed a special danger to human health, dedicated facilities would be required. If, however, experience demonstrated that the drug product did not pose such a risk, or if changes in manufacturing technology greatly reduced the risk, dedicated facilities might no longer be required.

V. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VI. Paperwork Reduction Act of 1995

This proposed rule contains information collections which are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (Pub. L. 104–13). The title, description, and respondent description of the information collection are shown below with an estimate of the annual reporting and recordkeeping burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.

Title: Current Good Manufacturing Practice; Proposed Amendment of Certain Requirements for Finished Pharmaceuticals.

Description: FDA is proposing to amend its CGMP regulations to establish procedures and specifications for testing, sampling, and other quality control activities; to establish criteria for initiating and performing out-of-specification investigations; and to control chemical and physical contaminants. These amendments would clarify certain manufacturing, quality control, and documentation requirements and ensure that the regulations more accurately encompass CGMP. In addition, the agency is updating the requirements for process and methods validation to incorporate guidance previously issued to industry and to reflect current practice. These proposed changes are intended to enhance the integrity of the drug manufacturing process and the safety of drug products. The total recordkeeping requirements are estimated at 89,884 hours, as a one-time reporting burden.

Description of Respondents: Businesses or other for profit and small businesses or organizations.

Estimated Reporting Burden[1]					
CFR Section	Number of Respondents	Responses per Respondent	Total Annual Responses	Hours Per Response	Total Hours
211.160(b) and (b)(1)	1,077	1	1	8.2	8,871
211.192(a)	4,184	1	1	6.7	28,060
211.192(b)	4,184	1	1	9.6	40,156
211.240	2,205	1	1	6.3	12,797
Total					89,884

[1] Because some of the numbers underlying these estimates have been rounded, figures in this table are approximate. There are no maintenance and operation costs nor start up and capital costs. The chart represents a one time burden.

As required by section 3507(d) of the Paperwork Reduction Act of 1995, FDA has submitted a copy of this proposed rule to OMB for its review of these previously approved information collection requirements. The agency solicits comments on the information collection requirements in order to: (1) Evaluate whether the proposed collection of information is necessary for the proper performance of the functions of the agency, including whether the information will have practical utility; (2) evaluate the accuracy of the agency's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) enhance the quality, utility, and clarity of the information to be collected; and (4) minimize the burden of the collection of information on those who are to respond, including through the use of appropriate automated, electronic, mechanical, or other technological collection techniques or other forms of information technology, e.g., permitting electronic submission of responses. Organizations and individuals desiring to submit comments on the information collection requirements should direct them to the Office of Information and Regulatory Affairs, OMB, New Executive Office Bldg., rm. 10235, 725 17th St. NW., Washington, DC 20503, Attention: Desk Officer for FDA.

VII. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (Pub. L. 96–354). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this proposed rule is consistent with the regulatory philosophy and principles identified in the Executive Order. The detailed data for the cost analysis were developed by Eastern Research Group, Inc., under contract to FDA, and their full report is on file at the Dockets Management Branch (address above).

The proposed changes to the CGMP regulations will affect manufacturers of finished human and veterinary pharmaceuticals, including medical gases, and repackers and relabelers of drug products. The majority of the proposed changes clarify existing manufacturing, quality control, and documentation requirements and represent current industry practice for the majority of firms. As such, they will have little or no economic impact on the majority of the industry. Some firms are not, however, operating in conformance with CGMP and the estimates represent the agency's best assessment of the incremental increase in costs that these firms would incur in implementing full compliance with the proposed changes.

The total cost is estimated to be a one-time expenditure of $2,900,000 ($0.7 million annualized over 5 years at a 7 percent discount rate). These costs would be generated by proposed changes that would require some manufacturers to revise existing, or develop new, standard operating procedures.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact on small entities. Because this regulation will not impose significant new costs on a large number of drug manufacturing operations, the agency certifies that the proposed rule will not have a significant economic impact on a substantial number of small entities. The agency estimates that, to comply with the proposal, establishments will incur additional annualized costs ranging from approximately $60 to $450 for establishments with fewer than 100 employees and from approximately $175 to $600 for establishments with 250 or more employees. For individual establishments, the impact of the proposal will depend on numerous factors, such as the type of establishment, the level of current conformance with the proposed changes, and the number and nature of products produced. Provisions of this proposal represent the most cost-effective option evaluated. Several of the rejected alternatives considered (such as revisions to § 211.84(d)(2) and (d)(3)) would have increased total costs by $14 to $27 million.

As a result of its analysis, FDA has determined that the proposed revision to the CGMP regulations for human and veterinary pharmaceuticals is not a significant regulatory action as defined by Executive Order 12866, and that the proposal will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

VIII. Effective Date

FDA proposes that any final rule that may issue based on this proposal become effective 90 days after the date of its publication in the Federal Register.

IX. Request For Comments

Interested persons may, on or before August 1, 1996, submit to the Dockets Management Branch (address above) written comments regarding this proposal. Two copies of any comments are to be submitted except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a. m. and 4 p.m., Monday through Friday.

X. References

The following references, which have been consulted in the drafting of this proposed rule, are readily and publicly available in a variety of locations. They have also been placed on display in the Dockets Management Branch (address

above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Juran, *Quality Control Handbook*, 4th ed., McGraw-Hill, 1988.

2. Pharmaceutical Manufacturers Association's (now known as Pharmaceutical Research and Manufacturers of America) Validation Advisory Committee, ''Process validation concepts for drug products,'' *Pharmaceutical Technology*, September 1985, p. 82.

List of Subjects

21 CFR Part 210

Drugs, Packaging and containers.

21 CFR Part 211

Drugs, Labeling, Laboratories, Packaging and containers, Prescription drugs, Reporting and recordkeeping requirements, Warehouses.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR parts 210 and 211 be amended as follows.

PART 210—CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURING, PROCESSING, PACKING, OR HOLDING OF DRUGS; GENERAL

1. The authority citation for 21 CFR part 210 continues to read as follows:

Authority: Secs. 201, 501, 502, 505, 506, 507, 512, 701, 704 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 355, 356, 357, 360b, 371, 374).

2. Section 210.3 is amended by adding new paragraphs (b)(23) through (b)(30) to read as follows:

§ 210.3 Definitions.

* * * * *

(b) * * *

(23) *Validation protocol* means a written plan describing the process to be validated, including production equipment, and how validation will be conducted, including objective test parameters, product and/or process characteristics, predetermined specifications, and factors which will determine acceptable results.

(24) *Process validation* means establishing, through documented evidence, a high degree of assurance that a specific process will consistently produce a product that meets its predetermined specifications and quality characteristics.

(25) *Methods validation* means establishing, through documented evidence, a high degree of assurance that an analytical method will consistently yield results that accurately reflect the quality characteristics of the product tested.

(26) *Equipment suitability* is the established capacity of process equipment and ancillary systems to operate consistently within established limits and tolerances.

(27) *Process suitability* is the established capacity of the manufacturing process to produce effective and reproducible results consistently.

(28) *Out-of-specification* means an examination, measurement, or test result that does not comply with preestablished criteria, as required by § 211.160(b) of this chapter.

(29) *Reprocessing* is a system of reworking batches that do not conform to standards or specifications. It includes the steps taken to ensure that the reprocessed batches will conform to all established standards, specifications, and characteristics. It includes a step or steps in the manufacturing process that are out of the normal processing sequence or that are not specifically provided for in the process.

(30) *Manufacturing process* means manufacturing and storage steps in the creation of the finished product from the weighing of components through the storing, packaging, and labeling of the finished product. Such steps include, but are not limited to, the following: Mixing, granulating, milling, molding, formulating, lyophilizing, tableting, encapsulating, coating, sterilizing, and filling.

PART 211—CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS

3. The authority citation for 21 CFR part 211 continues to read as follows:

Authority: Secs. 201, 501, 502, 505, 506, 507, 512, 701, 704 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 355, 356, 357, 360b, 371, 374).

4. Section 211.22 is amended by adding a sentence at the end of paragraph (a) to read as follows:

§ 211.22 Responsibilities of quality control unit.

(a) * * * The quality control unit shall be responsible for the review and approval of validation protocols and for the review of changes in product, process, equipment, or other changes to determine if and when revalidation is warranted.

* * * * *

§ 211.42 [Amended]

5. Section 211.42 *Design and construction features* is amended by removing paragraph (d).

6. Section 211.68 is amended by revising the fifth sentence in paragraph (b) to read as follows:

§ 211.68 Automatic, mechanical, and electronic equipment.

* * * * *

(b) * * * In such instances, a written record of the program shall be maintained along with data establishing proper performance. * * *

7. Section 211.82 is amended by revising the first sentence in paragraph (b) to read as follows:

§ 211.82 Receipt and storage of untested components, drug product containers, and closures.

* * * * *

(b) Components, drug product containers, and closures shall be stored under quarantine until they have been tested or examined and released. * * *

8. Section 211.84 is amended by revising paragraph (c)(1), by removing in paragraph (c)(5) the word ''data'' and adding in its place the word ''date'', and by removing in the first sentence of paragraph (d)(3) the word ''conformance'' and adding in its place the word ''conformity'' and removing the word ''procedures'' and adding in its place the word ''specifications'' to read as follows:

§ 211.84 Testing and approval or rejection of components, drug product containers, and closures.

* * * * *

(c) * * *

(1) The containers of components selected shall be cleaned in a manner to prevent introduction of contaminants into the raw material.

* * * * *

9. Section 211.101 is amended by revising paragraph (c)(3) and by adding new paragraph (c)(4) to read as follows:

§ 211.101 Charge-in of components.

* * * * *

(c) * * *

(3) The containers are properly identified; and

(4) The components conform to the quality specifications for the intended drug product.

* * * * *

10. Section 211.103 is amended by adding a new sentence to the end of the paragraph to read as follows:

§ 211.103 Calculation of yield.

* * * There shall also be a written production and control procedure for investigating any discrepancies in yield outside the maximum or minimum percentages established in master production and control records.

11. Section 211.110 is amended by redesignating paragraph (d) as paragraph (e) and by adding new paragraphs (d) and (f) to read as follows:

§ 211.110 Sampling and testing of in-process materials and drug products.

* * * * *

(d) When blend uniformity testing is needed to determine blend homogeneity, the sample size in both validation and ordinary production batches should approximate the dosage size. Sampling shall be demonstrated through validation to be representative of all portions of the blend.

* * * * *

(f) Validation of manufacturing processes required by this section shall be conducted in accordance with § 211.220.

12. Section 211.111 is amended by revising the first sentence to read as follows:

§ 211.111 Time limitations on production.

When appropriate, the manufacturer shall establish and validate maximum time limits for each phase of production as part of validation procedures required under § 211.220. * * *

13. Section 211.113 is amended by revising the last sentence in paragraph (b) to read as follows:

§ 211.113 Control of microbiological contamination.

* * * * *

(b)* * * Such procedures shall include validation of any sterilization or aseptic process.

14. Section 211.160 is amended by revising the first sentence in the introductory text of paragraph (b) and the first sentence in paragraph (b)(1) to read as follows:

§ 211.160 General requirements.

* * * * *

(b) Laboratory control shall include the establishment of scientifically sound and applicable written specifications, standards, sampling plans, and test procedures including resampling, retesting, and data interpretation procedures designed to ensure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity. * * *

(1) Determination of conformity to applicable written specifications for the acceptance of each lot within each shipment of components, drug product containers, closures, and labeling used in the manufacture, processing, packing, or holding of drug products. * * *

* * * * *

§ 211.165 [Amended]

15. Section 211.165 *Testing and release for distribution* is amended by removing paragraph (e) and redesignating paragraph (f) as paragraph (e).

16. Section 211.166 is amended by redesignating paragraphs (c) and (d) as paragraphs (d) and (e), respectively, and by adding new paragraph (c) to read as follows:

§ 211.166 Stability testing.

* * * * *

(c) After the expiration date has been determined, there shall be an ongoing testing program for each drug product to ensure product stability. At least one batch of each drug product shall be added to the stability program annually.

* * * * *

§ 211.176 [Removed]

17. Section 211.176 *Penicillin contamination* is removed.

18. Section 211.180 is amended by revising paragraph (a) to read as follows:

§ 211.180 General requirements.

(a) Any production, control, validation, or distribution record that is required to be maintained in compliance with this part and is specifically associated with a batch of a drug product shall be retained for at least 1 year after the expiration date of the last batch produced with that validated process or, in the case of certain OTC drug products lacking expiration dating because they meet the criteria for exemption under § 211.137, 3 years after distribution of the batch.

* * * * *

19. Section 211.192 is revised to read as follows:

§ 211.192 Production, control, and laboratory record review and investigation of discrepancies.

(a) Written procedures shall be established and followed requiring the review and approval by the quality control unit of all drug product production, control, and laboratory records, including packaging and labeling, to determine compliance with all established and approved written procedures and specifications before a batch is released or distributed.

(b) Written procedures shall be established and followed requiring the thorough investigation of any unexplained discrepancy (including a percentage of theoretical yield exceeding the maximum or minimum percentages established in master production and control records) or the failure of a batch or any of its components or in-process materials to meet any of its specifications (including any out-of-specification test result), whether or not the batch has already been distributed. The investigation shall extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy. Such procedures shall include:

(1) Procedures for attempting to identify the cause of the failure or discrepancy.

(2) Criteria for determining whether out-of-specification results were caused by sampling or laboratory error.

(3) Scientifically sound procedures and criteria for the exclusion of any test data found to be invalid due to laboratory or sampling error.

(4) Scientifically sound procedures and criteria for additional sampling and testing, if necessary, during the investigation.

(5) Procedures and criteria for extending the investigation to other batches or other products.

(6) Procedures for review and evaluation of the investigation, including all test results, by the quality control unit, to ensure a thorough investigation.

(7) Criteria for final approval or rejection of the batch involved, and for taking action on other batches and products if indicated by the investigation.

(c) A written record of the investigation shall be made and shall include:

(1) The reason for the investigation.

(2) A description of the investigation made, including all laboratory tests.

(3) The results of the investigation, including all laboratory test results involved in the investigation.

(4) Scientifically sound and appropriate justification for excluding any out-of-specification laboratory result found to be invalid.

(5) If laboratory results are found to be invalid, the subsequent laboratory results supporting the final determination of the tested item's conformity to all appropriate specifications for acceptance.

(6) The conclusions and subsequent actions concerning all batches and products that may have been associated with the failure or discrepancy.

(7) The signature(s) and date(s) of the person(s) responsible for approving the record of the investigation.

(8) The signature(s) and date(s) of the person(s) responsible for the final decision on disposition of the batch, and on other batches and products involved.

20. New subpart L, consisting of §§ 211.220 and 211.222, is added to read as follows:

Subpart L—Validation

Sec.
211.220 Process validation.
211.222 Methods validation.

Subpart L—Validation

§ 211.220 Process validation.

(a) The manufacturer shall validate all drug product manufacturing processes including, but not limited to, computerized systems that monitor and/or control the manufacturing process. The manufacturing process includes all manufacturing steps in the creation of the finished product including, but not limited to, the following procedures: Cleaning, weighing, measuring, mixing, blending, compressing, filling, packaging, and labeling.

(b) Validation protocols that identify the product and product specifications and specify the procedures and acceptance criteria for the tests to be conducted and the data to be collected during process validation shall be developed and approved. The protocol shall specify a sufficient number of replicate process runs to demonstrate reproducibility of the process and provide an accurate measure of variability among successive runs. Validation documentation shall include evidence of the suitability of materials and the performance and reliability of equipment and systems. The manufacturer shall document execution of the protocol and test results.

(c) The manufacturer shall design or select equipment and processes to ensure that product specifications are consistently achieved. The manufacturer's determination of equipment suitability shall include testing to verify that the equipment is capable of operating satisfactorily within the operating limits required by the process. Process suitability shall include documented rigorous testing to demonstrate the effectiveness and reproducibility of the process. Parts of the process that may cause variability or otherwise affect product quality shall be tested.

(d) There shall be a quality assurance system in place which requires revalidation whenever there are changes in packaging, component characteristics, formulation, equipment, or processes, including reprocessing, that could affect product effectiveness or product characteristics, and whenever changes are observed in product characteristics.

§ 211.222 Methods validation.

The accuracy, sensitivity, specificity, and reproducibility of test methods used by a manufacturer shall be validated and documented. Such validation and documentation shall be accomplished in accordance with § 211.194(a)(2).

21. New subpart M, consisting of § 211.240, is added to read as follows:

Subpart M—Contamination

Sec.
211.240 Control of chemical and physical contaminants.

Subpart M—Contamination

211.240 Control of chemical and physical contaminants.

(a) The manufacturer shall implement written procedures designed to prevent objectionable chemical and physical contamination, including cross-contamination.

(b) Dedicated production, which may include facilities, air handling equipment, and/or process equipment, shall be employed where contaminants, such as penicillin, pose a special danger to human or animal health or if there are no reasonable methods for the cleaning and removal of drug substances and/or component residues from buildings, facilities, and equipment.

(c) If a reasonable possibility exists that a drug has been exposed to cross-contamination, the manufacturer shall test the product for the presence of the potential contaminant. The manufacturer shall establish appropriate limits for such potential contaminants. Products that exceed the established limits shall not be released for distribution.

Dated: March 29, 1996.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 96–11094 Filed 5–2–96; 8:45 am]

BILLING CODE 4160–01–F