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21 CFR 210 and 21 CFR 211**

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Facts About Current Good Manufacturing Practices (cGMPs)

Current Good Manufacturing Practices (cGMPs) for human pharmaceuticals affect every American. Consumers expect that each batch of medicines they take will meet quality standards so that they will be safe and effective. Most people, however, are not aware of cGMPs, or how FDA assures that drug manufacturing processes meet these basic objectives. Recently, FDA has announced a number of regulatory actions taken against drug manufacturers based on the lack of cGMPs. This paper discusses some facts that may be helpful in understanding how cGMPs establish the foundation for drug product quality.

What are cGMPs?

cGMP refers to the Current Good Manufacturing Practice regulations enforced by the US Food and Drug Administration (FDA). cGMPs provide for systems that assure proper design, monitoring, and control of manufacturing processes and facilities. Adherence to the cGMP regulations assures the identity, strength, quality, and purity of drug products by requiring that manufacturers of medications adequately control manufacturing operations.

This includes establishing strong quality management systems, obtaining appropriate quality raw materials, establishing robust operating procedures, detecting and investigating product quality deviations, and maintaining reliable testing laboratories.

This formal system of controls at a pharmaceutical company, if adequately put into practice, helps to prevent instances of contamination, mix-ups, deviations, failures, and errors. This assures that drug products meet their quality standards.

The cGMP requirements were established to be flexible in order to allow each manufacturer to decide individually how to best implement the necessary controls by using scientifically sound design, processing methods, and testing procedures. The flexibility in these regulations allows companies to use modern technologies and innovative approaches to achieve higher quality through continual improvement. Accordingly, the "c" in cGMP stands for "current," requiring companies to use technologies and systems that are up-to-date in order to comply with the regulations. Systems and equipment that may have been "top-of-the-line" to prevent contamination, mix-ups, and errors 10 or 20 years ago may be less than adequate by today's standards.

It is important to note that cGMPs are minimum requirements. Many pharmaceutical manufacturers are already implementing comprehensive, modern quality systems and risk management approaches that exceed these minimum standards.

Why are cGMPs so important?

A consumer usually cannot detect (through smell, touch, or sight) that a drug product is safe or if it will work. While cGMPs require testing, testing alone is not adequate to ensure quality. In most instances testing is done on a small sample of a batch (for example, a drug manufacturer may test 100 tablets from a batch that contains 2 million tablets), so that most of the batch can be used for patients rather than destroyed by testing.

Therefore, it is important that drugs are manufactured under conditions and practices required by the cGMP regulations to assure that quality is built into the design and manufacturing process at every step. Facilities that are in good condition, equipment that is properly maintained and calibrated, employees who are qualified and fully trained, and processes that are reliable and reproducible, are a few examples of how cGMP requirements help to assure the safety and efficacy of drug products.

How does FDA determine if a company is complying with cGMP regulations?

FDA inspects pharmaceutical manufacturing facilities worldwide using scientifically and cGMP- trained individuals whose job it is to evaluate whether the company is following the cGMP regulations. FDA also relies upon reports of potentially defective drug products from the public and the industry. FDA will often use these reports to identify sites for which an inspection or investigation is needed. Most companies that are inspected are found to be fully compliant with the cGMP regulations.

If a manufacturer is not following cGMPs, are drug products safe for use?

If a company is not complying with cGMP regulations, any drug it makes is considered "adulterated" under the law. This kind of adulteration means that the drug was not manufactured under conditions that comply with cGMP. It does not mean that there is necessarily something wrong with the drug.

For consumers currently taking medicines from a company that was not following cGMPs, FDA usually advises these consumers not to interrupt their drug therapy, which could have serious implications for their health. Consumers should seek advice from their health care professionals before stopping or changing medications. Regulatory actions against companies with poor cGMPs are taken as a preventive measure because the manufacturing processes do not meet FDA's regulatory standards.

By focusing on the procedures and processes used to make these drugs, FDA is working to ensure that drugs meet their quality standards and are safe and effective. The impact of cGMP violations depends on the nature of those violations and on the specific drugs involved. A drug manufactured in violation of cGMP may still meet its labeled specifications, and the risk that the drug is unsafe or ineffective could be minimal.

Thus, FDA's advice will be specific to the circumstances, and health care professionals are best able to balance risks and benefits and make the right decision for their patients.

What can FDA do to protect the public when there are cGMP violations?

If the failure to meet cGMPs results in the distribution of a defective drug, the company may subsequently recall that product. This protects the public by removing these drugs from the market. While FDA cannot force a company to recall a drug, companies will usually recall voluntarily or at FDA's request. If a company refuses to recall a drug, FDA can warn the public and could seize the drugs that are on the market.

Even if the drugs are not defective, FDA can bring a seizure or injunction case in court to address cGMP violations. When FDA brings a seizure case, the agency asks the court for an order that allows federal officials to take possession of "adulterated" drugs and destroy them. This enables FDA to immediately prevent a company from distributing those drugs to consumers.

When FDA brings an injunction case, FDA asks the court to order a company to stop violating cGMPs. Both seizure and injunction cases often lead to court orders that require companies to take many steps to correct cGMP violations, such as hiring outside experts, writing new procedures, and conducting extensive training of their employees. FDA can also bring criminal cases because of cGMP violations, seeking fines and jail time.

How would a new drug company learn about cGMPs and about FDA's expectations on complying with them?

FDA publishes regulations and guidance documents for industry in the Federal Register. This is how the federal government notifies the public of what we are doing and how we do it. FDA's website, www.fda.gov also contains links to the cGMP regulations, guidance documents, and various resources to help drug companies comply with the law.

FDA also conducts extensive public outreach through presentations at national and international meetings and conferences, to discuss and explain the cGMP requirements, the latest policies, and the Agency's expectations. Guidance on the cGMP regulations can also be obtained through FDA's

Small Business Representatives that are located throughout the country, through FDA District Offices, and from the Center for Drug Evaluation and Research, Office of Compliance, Division of Manufacturing and Product Quality.

THE NEXT SECTION IS THE PREAMBLE

THE FOLLOWING SECTION IS THE PREAMBLE

Title 21--Food and Drugs

CHAPTER I--FOOD AND DRUG ADMINISTRATION DEPARTMENT
OF HEALTH, EDUCATION, AND WELFARE

SUBCHAPTER C--DRUGS: GENERAL

[Docket No. 75N-0339] HUMAN AND VETERINARY DRUGS
Current Good Manufacturing Practice in Manufacture,
Processing, Packing, or Holding

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: This document amends the FDA regulations that set forth current good manufacturing practice (CGMP) for human and veterinary drug products. The amendments update present regulations in light of current technology for drug manufacturing and delineate requirements more specifically than do the present regulations. Although some of the provisions in these amendments represent requirements not specifically included in the existing CGMP regulations, in many instances the revisions are practices that have been considered implicit in the regulations or are at least considered by most manufacturers to be desirable requirements for their own operations. Under the Federal Food, Drug, and Cosmetic Act, a drug is deemed to be adulterated unless the methods used in its manufacture, processing, packing, and holding, and the facilities and controls used therefor, conform to current good manufacturing practice so that the drug meets the safety requirements of the act and has the identity and strength and meets the quality and purity characteristics that it is represented to have. The regulations are being updated and made more explicit, and therefore less subject to varying interpretations, to assure that all members of the drug industry are made aware of the level of performance expected of them to be in compliance with the act.

EFFECTIVE DATE: March 28, 1979.

FOR FURTHER INFORMATION CONTACT:

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SUPPLEMENTARY INFORMATION: In the FEDERAL REGISTER of February 13, 1976 (41 FR 6878), the Commissioner of Food and Drugs proposed to revise the CGMP regulations, Parts 210 and 211 (21 CFR Parts 210 and 211), issued under section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351(a)(2)(B)), to update them in light of current technology and to adopt more specific requirements to assure the quality of finished drug products. Because of the nature and extent of the proposed revisions, the Commissioner allowed until June 14, 1976, for interested persons to submit comments. The Commissioner received comments from 168 respondents totaling approximately 2,000 pages. These comments represent many interests--individual consumers; nonprofit institutions or associations; health-care departments of hospitals, colleges, and universities; State and foreign health-care organizations; domestic and foreign drug manufacturers, repackers, and distributors; consultants to the drug industry; drug equipment manufacturers; and numerous trade and professional associations representing manufacturers, repackers, distributors, consulting engineers, and professionals in the health-care system.

In general, the comments supported the Commissioner's concern for the availability of uniformly high quality drug products. Consumers, in particular, expressed strong support for the proposed revisions, especially the provisions for expiration dating of pharmaceuticals. A majority of drug manufacturers agreed with many of the proposed revisions, but objected to others. A few manufacturers objected to most

of the proposal. The Commissioner is pleased to note that where differences existed, many interested persons furnished alternative wording and justification in support of such alternatives. The Commissioner has carefully considered every comment and all suggested alternatives. The final regulation, set forth below, adopts a number of the recommendations submitted. Certain other recommendations, not adopted at this time, may be considered in any future proposed revisions. During the past several years, the FDA has issued a number of FEDERAL REGISTER documents relating to CGMP regulations, specifically Parts 210 and 211. The following summary will help clarify the status of these various documents. 1. A proposal on returned and salvaged drug products appeared in the FEDERAL REGISTER of January 16, 1975 (40 FR 2822) and was repropoed as 211.208 (21 CFR 211.208) in the FEDERAL REGISTER of February 13, 1976 (41 FR 6870). Comments on both proposals were reviewed and considered in preparing the final regulations set forth in Part 211 below. 2. A proposal on CGMP regulations for human and veterinary drugs appeared in the FEDERAL REGISTER of February 13, 1976 (41 FR 6878). That proposal is the basis for the subject final regulations and included proposed revisions in 201.17, 207.3, 207.20, and Parts 210 and 211, and revocation of 229.25. 3. A final regulation in the FEDERAL REGISTER of April 23, 1976 (41 FR 16932) amended Part 211 (CGMP regulations) by eliminating reference to glass-fiber filters. It, therefore, eliminated the need for further comments on the February 13, 1976, proposal regarding such filters because all references to glass fiber-containing filters would be deleted from the final regulation. 4. A proposal on CGMP regulations for large volume parenteral drug products (LVP) for human use was published in the FEDERAL REGISTER of June 1, 1976 (41 FR 22202).

The proposal would add a new Part 212. Comments were due by September 29, 1976 and are under review. 5. A request for comments and information regarding small volume parenteral drug products (SVP) was published in the FEDERAL REGISTER

of June 1, 1976(41 FR 22219), and the time for submitting comments was extended to October 29, 1976 by notice in the FEDERAL REGISTER of September 10, 1976 (41 FR 38540). Comments are being reviewed, and a specific proposal may be published in the future. The comments and recommendations regarding the January 16, 1975 and February 13, 1976 proposals, the April 23, 1976 amendment to the latter proposal, and the Commissioner's conclusions concerning them are set out below.

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I. GENERAL COMMENTS

1. Many comments were received regarding the need for the proposed changes in the CGMP regulations. A number of comments from individual consumers, a State consumer services organization, and a national association of health-care professionals strongly favored new or revised regulations that would improve the level of assurance that marketed drug products meet high quality standards.

Many other comments, particularly from manufacturers and trade associations, generally supported the desirability of CGMP regulations, but objected to specific provisions of the proposal and questioned whether a favorable cost-benefit ratio justified implementing some of the proposed provisions. But some manufacturers, particularly smaller firms, objected to the proposed changes, maintaining that drug quality would not be improved by the proposed changes and that the costs outweigh any benefits.

The need and rationale for an overall revision and for specific changes in the CGMP regulations are discussed at length in the preamble to the February 13, 1976 proposal. Briefly summarizing this discussion, the technological advances and the general upgrading of drug quality assurance by most manufacturers since the CGMP regulations were promulgated in 1963 and last updated in 1971 mean that the "current good manufacturing practice" reflected in the existing regulations are no longer "current" in many respects and are not suited to current manufacturing techniques.

In addition, many requirements prompted questions about interpretation, vagueness, and omissions. The proposal was intended to solve many of these problems. Interested persons were urged to review the proposal carefully, to identify any areas that might require clarification or modification, and to submit reasoned comments with suggested alternative language.

The period provided for public comment was 120 days instead of the usual 60 days because of the length of the proposal; the novel, controversial, or complex nature of some of the proposed provisions; and the desire to give affected persons ample time for review and preparation of extensive comments. Having reviewed the preamble of the February 13, 1976, proposal and the extensive comments, the Commissioner is satisfied that an updating of the CGMP regulations is necessary and desirable. Therefore, most of the February 13, 1976, proposal has been adopted, but with numerous textual changes, many of which are based upon alternative language suggested in the comments.

In evaluating each comment, the Commissioner considered whether drug product quality would be assured, compromised, or unaffected by the adoption or deletion of a regulation, as well as whether it reflected a current practice in the industry and its benefits appeared to outweigh its costs.

The Commissioner is promulgating those regulations embodying contemporary practices that will maintain or improve the quality of pharmaceuticals without imposing unreasonable or excessive costs or other burdens on manufacturers. Modifications were adopted, or decisions were made not to finalize particular aspects of the proposal, in order to add flexibility for manufacturers, to relieve or eliminate unjustified cost burdens, or to clarify the requirements, without adversely affecting the best interests of the consumer.

The agency has completed a detailed cost analysis based on information submitted by interested persons who commented on the economic impact assessment of the proposal. This issue is discussed in a revised economic impact assessment available at the office of the Hearing Clerk, Food and Drug Administration. For the reasons set forth in the agency's economic impact assessment, it is believed that this final regulation will not cause major economic impact, as defined by

Executive Order 11821 (as amended by Executive Order 11949), and OMB Circular A-107.

2. A number of comments said the proposed CGMP regulations would impose rigid and inflexible standards that would curtail progress and discourage technological innovations. Others said the proposed regulations were so detailed that sound judgment by the manufacturers and by inspecting FDA investigators could not be used.

The Commissioner is keenly aware that the general CGMP regulations must apply to a wide variety of drug products. Therefore, the CGMP regulations in Part 211 are intended to be general enough to be suitable for essentially all drug products, flexible enough to allow the use of sound judgment and permit innovation, and explicit enough to provide a clear understanding of what is required.

The agency has received numerous inquiries requesting clarification of certain provisions, and it sought to remove ambiguities by this revision. In finalizing these revisions, the Commissioner has considered past experience, the purposes of the CGMP regulations, the need to balance specificity and clarity with flexibility in attaining these purposes, and the comments received in response to the proposal. A number of changes have been made in these final regulations to reflect the broad applicability of, to allow flexibility in, and to encourage innovation within the CGMP regulations.

The agency does intend to issue more specific CGMP regulations for unique classes of products as one means of clarifying these regulations. The Commissioner welcomes suggestions and petitions from interested persons who find deficiencies, excessive burdens, or inflexibility in these regulations and who identify innovative and more efficient ways to achieve the goals of these regulations.

3. A number of comments addressed the so-called "how to" versus the "what" argument; that is, the proposed CGMP regulations describe "how" a particular requirement should be achieved rather than specifying "what" it is that is to be achieved. Many comments recommended that the regulations establish only objectives or specifications and allow each manufacturer to determine the best method of attaining the objective or meeting the specification. For example, one comment proposed that FDA require positive identification of a person rather than specifying that a signature be used--this would allow use of other means of identifying a person, such as an identifying number or initials.

The Commissioner believes that, with relatively few exceptions, the CGMP regulations do describe "what" is to be accomplished and provide great latitude in "how" the requirement is achieved. For example, written records and procedures are required, but FDA will recognize as satisfactory any reasonable format that achieves the desired results. Because of the need for uniformity in certain areas of the CGMP regulations that have presented problems in the past, however, there are some instances where it is desirable to specify the manner in which requirements are to be accomplished.

In promulgating these regulations, the Commissioner carefully reconsidered the need for such specificity where it appears and adopted only those specific requirements that are fully justified.

4. One comment, filed by an FDA employee, recommended that self-inspection and performance auditing programs within the industry be a requirement under the CGMP regulations to assure the reliability of drug products and to prevent release of defective products.

The Commissioner finds that the concept of self-inspection and performance auditing has considerable merit. The

pharmaceutical industry has made great efforts to develop self-evaluation programs, frequently using a team of inspectors composed, at least in part, of people from outside the area or firm being audited. The scope, elements, and intensity of such programs, however, vary from elaborate detailed audits to rather superficial inspections conducted perhaps once a year.

The agency has considered such programs in the past, but has concluded that the essential elements of a beneficial program have not yet been sufficiently defined or tested. Moreover, because of the significant impact that a requirement for self-inspection would have on the industry and because only one comment regarding self-inspection was received, the Commissioner concludes that further public discussion is desirable before a specific proposal or regulation is issued.

5. One comment suggested that a product defect surveillance and reporting system requirement similar to the system developed and operated by the United States Pharmacopeia (U.S.P.) be a part of the CGMP regulations. The suggestion would require full participation by manufacturers, rather than voluntary participation, in a system of identifying defective products, removing them from the market, and investigating the cause of the defect.

The Commissioner notes that the Drug Product Defect Reporting System maintained by U.S.P. is designed to identify drug product complaints from various sources other than the manufacturer, such as pharmacies and hospitals, and to facilitate transmission of this information to the manufacturer and to FDA.

The value of such a reporting system is in its broad source of information. The CGMP regulations in part 211, however, apply only to manufacturers of drug products. Section 211.198 (21 CFR 211.198) addresses the handling of reports to the manufacturer about drug product defects and requires that

manufacturers investigate complaints that may have a bearing on drug product quality. Such information is subject to review by FDA.

6. Comments regarding the effect of these regulations on employee motivation were received from several interested persons.

While generally approving the technical aspects of the proposal, these comments expressed concern that employee morale may be stifled because of the "close supervision" or "independent verification" of their work mandated by some of the proposed requirements. The comments also expressed concern about the availability of qualified personnel in the health-care system and the ability of the industry to attract such qualified persons for relatively unimagined duties. They suggested that the use of a different instrument in the checking procedure would, in some instances, offer a better chance of detecting an error than would a system that relies upon independent verifications by different persons using the same instrument.

The Commissioner recognizes that employee interests and motivation play a major role in assuring drug product quality, as described in the preamble discussion for the proposed 211.25, relating to employee training, for example. Good employee morale and work motivation are highly desirable in any work situation. Because of potential employee resentment of an intensive "check system," the Commissioner has considered alternatives and the consequences of no independent verification.

The requirement for verification applies to functions that involve human judgment and consequently are susceptible to human error. The results of such errors, if undetected and uncorrected, can include, for example, improper formulations and improper release of drug products because of incorrect laboratory calculations. Independent verification is generally

considered a "current" practice, not only in the drug industry but elsewhere, as a way to reduce the risk of human error.

The intent of such a check is to verify that the procedure or work was performed. It is a necessary function in the manufacture of drug products and is already required in the existing CGMP regulations. The Commissioner believes that, while employees may not always welcome independent verification, most accept it as a condition of their particular assignments. Given the possible serious consequences of errors, the "check system" requirement does not seem to be an unjustified burden and, if properly explained, should not be perceived by employees negatively.

The use of separate instruments, where practicable, as an adjunct to independent verification by a second person, is a procedure that has merit. The Commissioner encourages the use of such a procedure, but has concluded that a separate instrument for independent measurements would be a costly and unnecessary requirement in the CGMP regulations. These regulations separately mandate an equipment calibration and maintenance program to assure proper performance and safeguard equipment accuracy.

7. Several comments indicated a general interest in bioavailability and bioequivalence requirements for drug products. Because of the importance of bioavailability and bioequivalence to safe and effective use of drug products, these comments encouraged FDA to issue regulations establishing necessary requirements to assure this type of product quality as soon as possible.

The Commissioner advises that bioavailability and bioequivalence requirements for drug products were addressed in separate proposals published in the FEDERAL REGISTER of June 20, 1975 (40 FR 26157 and 26164) and made final in the FEDERAL REGISTER of January 7, 1977 (42 FR 1624).

8. Several comments were received regarding written procedures to describe specific manufacturing and control operations.

In general the comments agreed that written procedures were suitable in many instances, but were not required for every operation involved in the production and control of drug products. Specific examples were cited as requiring excessive and unnecessary written procedures. The most common example cited was 211.67(b), which proposed, in part, that there be written procedures assigning responsibility for cleaning and maintenance and describing in detail the maintenance and cleaning schedules, the methods, equipment, and materials to be used, and the methods of disassembling and reassembling all equipment used in the manufacture, processing, packing, or holding of a drug product.

The objection to the requirement of this instance appears to be in reference to "all" equipment. The requirement for written procedures is intended to provide additional assurance of effective communication of appropriate information from firm management to line personnel and of regular performance of a firm's established programs and procedures. It is not enough that employees "know their jobs." Key personnel may be absent without warning; personnel substitutions involving less experienced employees may be necessary; and new or revised instructions to employees must be adequately conveyed to those who need to know.

These situations are not usual, but may occur frequently. The most appropriate method for reliably relating policies and procedures to those who must know them is to have them set down in writing, readily available, and presented in a manner easily understood. The Commissioner does not believe this is a burdensome requirement. The regulations do not require that a separate procedure be written for each and every individual piece of equipment. Thus, for example, similar pieces of equipment that would have the same cleaning schedule could

be considered together for convenience and would be in compliance with requirements of 211.67(b).

9. One comment suggested that written procedures are changed frequently and the regulations make no provisions for dating the written procedures and retaining outdated written procedures. The comment pointed out that the outdated procedures may be of some value in following up problems that may have occurred during the period that the written procedures were in effect.

The Commissioner has carefully considered the merits of this suggestion and concludes that specific provisions for the dating and retention for all written procedures are not needed at this time. The regulations already contain this type of requirement for certain records such as master and batch production control records. For other procedures, it is preferable for each manufacturer to develop his scheme for dating, replacing, and retaining written procedures.

10. One comment recommended that FDA provide a complete set of correct model forms for use by individual firms in their own recordkeeping. The comment suggested that the model forms could be a part of the CGMP regulations, or FDA could furnish such information separately. The Commissioner does not find sufficient need at this time to warrant development of such model forms. The CGMP regulations, as amended, provide sufficient detail for manufacturers to understand readily what is required for compliance with these regulations.

Because of the broad nature of the regulations and the wide variety of manufacturers subject to the CGMP regulations, the Commissioner is not convinced that model forms would be so adaptable as to be useful for a majority of firms. If, however, future experience with these CGMP regulations indicates that model forms issued as guidelines would be helpful, the Commissioner will reconsider the matter.

11. A respondent suggested promulgating the regulations under section 701(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 371(e)) to give opportunities for hearings on, and judicial review of, these regulations before they take final effect. The authority to promulgate the regulations for the enforcement of the current good manufacturing practice provisions of the act rests specifically in section 701(a) of the act.

As noted in paragraph 35, Congress voted in 1962 not to require that CGMP regulations be issued under the procedures set forth in section 701(e) of the act. The Commissioner could elect to follow a procedure similar to that in section 701(e) of the act and hold a legislative type of hearing on specific aspects of this proposal under 21 CFR Part 15. After an extensive review of the numerous comments, however, he has decided that there are no particular portions of this regulation which need a further presentation of information or arguments.

Any interested person may submit a petition under 21 CFR 10.30 to the Commissioner requesting such a hearing and should identify with specificity and supporting explanations the issues that might be heard. No such petition will, however, automatically delay the effective date of these regulations, as would be the situation under section 701(e) of the act; the Commissioner will grant a delay only if clearly justified.

12. In reference to the proposed requirement in 211.184(a), that the prime manufacturer, if known, be listed, one comment recommended that the CGMP regulations require that the name and lot number of the original manufacturer of the final drug product be part of the labeling.

The Commissioner recognizes that a number of interested persons have, at various times, recommended that the labeling of drugs (whether bulk or in dosage form) bear the name of the manufacturer in addition to the distributor or repacker or relabeler. Changes such as this, however, would have such

broad effect and would be likely to generate such enormous public and industry interest that the Commissioner does not believe that these final regulations are the proper place to consider them. Moreover, there are questions concerning the legality of such a requirement being adopted under section 501(a)(2)(B) of the act (21 U.S.C. 351(a)(2)(B)). Therefore, the Commissioner declines to act on this comment at this time.

II. TERMINOLOGY AND LANGUAGE IN THESE REGULATIONS

13. Numerous comments were received suggesting changes in language, grammar, terminology, punctuation, sentence structure, and other editorial changes to clarify or improve upon the requirements as stated in the regulations or to eliminate redundancies or inconsistencies. Those proposals that raised significant policy questions, suggested changes in the substance of the regulation, or otherwise required, in the Commissioner's opinion, a specific response, are discussed individually below. Many of the suggested changes, however, were more editorial and stylistic and do not warrant a detailed discussion that would double the length of this preamble. The Commissioner reviewed each of these numerous editorial and language changes to determine whether it offered an improvement in clarity or definition, eliminated an obvious error or redundancy, promoted consistency with other portions of the regulations, or otherwise identified textual problems that were not previously noted by FDA. Where the proposed alternative language or other changes suggested by them were superior to the proposal, they were adopted in substance or verbatim. Where they did not offer any improvement, the Commissioner declined to accept them.

14. One comment recommended consistent usage of the words "drug," "drug product," "phase," "step," and "stage." The comment suggested that confusion can result from using "drug" and "drug product" interchangeably because, in the technical literature, the term "drug" usually refers to the bulk drug and the term "drug product" to the finished dosage form. The comment also pointed out that the words "phase," "step," and "stage" are used interchangeably and may, in fact, describe different aspects of a production operation.

The Commissioner finds that Parts 210 and 211, as amended by this order, use "drug" and "drug product" consistently with the definitions in section 201(g) of the act and 210.3(b)(4) of

the regulations (21 CFR 210.3(b)(4)); that is, "drug products" refers to only finished dosage forms, while "drug" includes both bulk drugs and drug products. With regard to the words "phase," "step," and "stage," he finds that it is unnecessary to describe various aspects of a production operation by using different words that can have essentially the same meaning in common usage.

Therefore, for clarification, the CGMP regulations are revised to use the word "phase" consistently when describing certain aspects of the manufacturing operations.

15. A number of comments concerned use of the phrase "to prevent" throughout the proposed CGMP regulations. The phrase appears in these regulations to indicate that a required procedure must be accomplished, or accomplished in a manner, to preclude a resultant deleterious effect, e.g., "containers shall be opened, sampled, and resealed in a manner to prevent contamination." In several instances, the comments objected to the phrase as being "too absolute," stating that the regulations should allow for variation from the desired objective on occasion because no firm should be expected to prevent undesirable occurrences 100 percent of the time.

The phrase "designed to prevent" was suggested as an alternative. A number of comments objected to the phrase "to prevent" when used in conjunction with written procedures on the basis that written procedures in themselves do not prevent anything; they must be implemented to accomplish the desired objective. The phrase "designed to prevent" was again suggested as an alternative phrase. The Commissioner believes that it is not acceptable to allow deviations from practices that could result in adverse effects upon the quality of the drug product, even on occasion.

The Commissioner, however, does agree with the comments' contention that written procedures must be implemented to

prevent anything and has adopted the phrase "designed to prevent" in the applicable portions of the final regulations.

16. Several comments objected to the use of terminology such as "adequate," "appropriate," "significant," "major" equipment and "long" periods. The objection is that these terms lack the specificity needed and will result in confusion to the manufacturer.

The Commissioner has carefully considered the use of these words and other words and phrases that imply absolute requirements in judgmental matters. Except for the changes noted in responding to the comments by specific sections, he concludes that the terminology is appropriate as set forth in the regulations. Words such as "adequate" and "appropriate" do permit reasonable, albeit variable, interpretation by reasonable people, but are necessary and desirable for regulations to have both broad applicability and flexibility.

An overwhelming majority of those commenting on the proposal were greatly concerned that the regulations accommodate the wide variability of manufacturing and control systems. In fact, a number of comments recommended additional use of modifying words such as "appropriate" and "adequate" to carry a sense of flexibility in the CGMP regulations.

17. Several comments objected to the use of the word "current" in the title and text of the regulations. Other comments indicated that some of the proposed requirements, such as separation of penicillin operations in the production of veterinary drug products and the proposed statistical testing requirements, are not "current" good manufacturing practice for the industry. Another comment requested that the term "current" be defined.

One comment recommended that the word "current" be deleted since it is obvious that the latest regulations to be

published are current, and therefore the use of the word "current" is superfluous. Several of these comments reflect, the Commissioner believes, a misunderstanding regarding the use of the word "current."

The act itself, in section 501(a)(2)(B), specifies that a drug is deemed 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 the 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.

The Congress intended that the phrase itself have a unique meaning and that the good manufacturing practice regulations represent sound current methods, facilities, and controls for the production of drugs to assure safety, identity, strength, quality, and purity of the product.

The agency determines what constitutes "current good manufacturing practice" based upon its experience with the manufacture of drugs through inspectional and compliance activities; upon knowledge gained from reviewing new drug applications, antibiotic forms, biological product and establishment licenses, and other submissions to FDA; and upon consideration of comments from interested persons received in response to proposals to amend CGMP regulations. Although the practices must be "current" in the industry, they need not be widely prevalent.

Congress did not require that a majority or any other percentage of manufacturers already be following the proposed mandated practices, as long as it was a current good manufacturing practice in the industry, i.e., that it had been shown to be both feasible and valuable in assuring drug quality. The accumulated knowledge and experience of FDA in

the area of current good manufacturing practice is reflected in a body of information, which with the exception of trade secrets and information relating to pending enforcement actions has long been available to the public.

This body of information, which is the basis for agency expertise with respect to current good manufacturing practice, is so voluminous that formal inclusion into the administrative record of this proceeding is not practical. Nevertheless, the Commissioner relies on this body of information in promulgating this regulation.

The following list describes the information coming to FDA since active preparation of the proposal to revise the CGMP regulations began (in late 1974): (1) FDA investigators conducted approximately 20,000 inspections of establishments in which drugs for human use are processed, and another 6,000 inspections of veterinary drug establishments.

After each inspection, an FDA investigator filed an establishment inspection report with the agency. With rare exceptions (for cases subject to active law enforcement investigation), these reports are promptly available as public information under FDA's Freedom of Information regulations (21 CFR Part 20). (2) FDA received approximately 1,000 full new drug applications (including original submissions, resubmissions, and amendments), 1,500 abbreviated new drug applications, and 6,900 new animal drug applications.

Each application contains information pertaining to the manufacturing processes to be used in producing the drug subject to the application. In addition, about 10,000 supplements to approved applications, many relating to manufacturing processes, were submitted. FDA must review and approve these processes before an application may be approved. The contents of approved new drug applications, except those portions that constitute trade secrets, are

available for public inspection. (21 CFR 314.14, 431.71, 514.11, and 601.51.) (3)

FDA monitored more than 1,200 recalls of drugs for human use and 275 recalls of veterinary products. In each recall resulting from a product defect, FDA investigates to determine the manufacturing control problems that led to the defect. These investigations, generally embodied in establishment inspection reports, are also publicly available upon completion of regulatory activities. (4) FDA brought over 500 legal proceedings--criminal proceedings, seizures, and injunctions--involving drugs for human use and veterinary products.

Again, in those proceedings arising from product defects, a full investigation has been conducted to support the agency's case. In addition to the establishment inspection reports, testimony, documented evidence, and court papers are publicly available. Furthermore, FDA representatives have participated in numerous activities--meetings, seminars, and workshops (regarding CGMP's, industry practices, and agency policies)--with organizations such as Parenteral Drug Association, the Proprietary Association, the National Association of Pharmaceutical Manufacturers, Pharmaceutical Manufacturers Association, the Packaging Institute, University of Wisconsin Industrial Pharmacy Management Conference, and the American Society for Quality Control.

These activities further contribute to the knowledge and experience of FDA. Many of the organizations sponsoring these activities publish publicly available proceedings of these meetings, e.g., Journal of the Parenteral Drug Association and Proprietary Association Manufacturing Controls Seminar Presentations. For additional information summarizing FDA's activities for the past several years, see 1975-1977 Annual Reports and fiscal year 1979 Justification of Appropriation Estimates for Committee on Appropriations. (Copies have been placed on file with the office of the Hearing Clerk, FDA.)

18. Several comments asserted that CGMP regulations must reflect the "current" practices of manufacturers of a particular type of drugs. Others objected to the absence of findings specifically supporting the conclusion that a particular practice was a "current" practice of the manufacturers of a particular type of drug product. Among the drug products cited as the appropriate measure for current good manufacturing practice were veterinary drugs, medical gases, radio-pharmaceuticals, and cosmetic-type drug products.

The Commissioner recognizes that different types of drug products may require specialized manufacturing and control procedures or may not be appropriate to the application of certain procedures that are otherwise generally applicable to drug products. For this reason, he has announced his intention to issue specialized current good manufacturing practice regulations for particular types of drug products and, in fact, has already issued one such proposal regarding large volume parenteral drug products.

The regulations set forth in Part 211 (21 CFR Part 211) are designed to be applicable to all drug products in finished dosage form. They are based on practices widely used throughout the industry for manufacture of many finished drug products. The Commissioner rejects the idea that FDA must establish that each CGMP requirement is a current practice of the manufacturers in each subset of drug products covered by the general requirements of Part 211.

As noted elsewhere in this preamble, the Commissioner has evaluated whether this requirement is appropriate for particular types of drug products in response to specific comments. Where he has found it to be inappropriate, he has exempted the products from the requirement; otherwise the Commissioner has concluded that all manufacturers of finished drug products should be subject to the requirements of Part 211. The Commissioner believes this is the only feasible way to

approach such general current good manufacturing practice regulations.

There is no consensus on the various subgroups of finished drug products, and therefore a requirement that the currency of practice must be documented for each subgroup would ultimately amount to establishing that it was a current practice by each manufacturer of each drug product, a burden which would be impossible to establish and unnecessary for purposes of regulation. Therefore, the Commissioner rejects these comments.

III. AMENDMENTS REGARDING PLACEMENT OF EXPIRATION DATE ON DRUG PRODUCT LABELS

19. A substantial number of comments objected to the proposed requirement in 201.17 that the expiration date appear on the shipping carton. The majority objected on the grounds that it is common practice for shipping containers to contain different drug products or similar drug products with different expiration dates. Some persons recommended that the expiration date be required on the shipping carton only when the carton is for one drug product.

The Commissioner recognizes that there are valid reasons for comingling various drug products, or different lots of the same drug product, within a single shipping carton. In such instances it may not always be practical for each different expiration date to appear on the shipping carton.

Because of significant differences in the use and labeling of shipping cartons, the Commissioner concludes that a requirement for the expiration date to appear on the shipping carton when such shipping carton is not the immediate container should not be a part of the regulations at this time, and this requirement is deleted from 201.17. Manufacturers are encouraged, however, to provide appropriate information to the extent possible on all shipping cartons to facilitate handling, reduce the possibility of mixups, and allow easy identification of lots that are being recalled or withdrawn from the marketplace.

20. Several comments were received regarding expiration dating of shipping cartons containing radio-pharmaceuticals. Generally, the comments were that such drugs usually have several separate component parts each with a different expiration date. One comment requested an exemption from the entire section, while another comment asked for an exemption for the shipping carton. The Commissioner believes

that 201.17, as revised, will accommodate the special problems encountered in the handling of radiopharmaceuticals.

21. Several comments suggested that the heading of this section be revised by changing the title word from "drugs" to "drug product" to conform to the drug product definition in 210.3(b)(4). The Commissioner finds that the word "drugs" in the heading of 201.17 is more consistent with the terminology used in Part 201. The term "drug product," as defined in 210.3(b)(4), is intended specifically for use in Part 211 to convey a meaning more limited than the general term "drug" as defined in section 201(g) of the act. However, to clarify that 201.17 applies to drug products under Parts 210 and 211, the final regulation in 201.17 is revised to refer to both drugs and drug products.

22. A number of comments recommended that the expiration date not be required on outer retail package labeling, such as display cartons, if the expiration date appearing on the immediate container is visible. The Commissioner agrees that it was his intention to require that the expiration date be visible under usual and customary conditions of packaging. He notes that section 201(k) of the act provides for label information that is easily legible through the outside container or wrapper. Section 201.17 is revised to allow such alternative placement of the expiration date.

23. One comment said the proposed section does not clearly cover a situation where the producer does not package the material in a retail package, but markets drug products in bulk containers. Although the Commissioner believes that the situation described is covered by the proposed regulations, the final regulation as rewritten clearly specifies that when the expiration date of a drug, including drug products, is required, it shall appear on the immediate container. There is no exemption for drug products in bulk containers.

24. One comment recommended that 201.17 specifically exclude "wrappers" for individual tablets, lozenges, and suppositories from the requirement of bearing an expiration date. The Commissioner finds that it is generally understood that protective wrappers for individual dosage forms that are further packaged in immediate containers are not required to bear an expiration date. Because only one comment about protective wrappers was received requesting a statement in the regulations and no information was submitted that the issue raised has actually been a problem, the Commissioner concludes that further clarification of this section is not now warranted.

25. Several comments asked about the acceptability of placing the expiration date on the crimp of the drug product tube. Because of the wide variety of available methods and techniques of applying and presenting expiration dating information on the immediate container, the Commissioner has not attempted to specifically evaluate and list individual methods. In general, he finds that the expiration date should be readily seen under usual and customary circumstances. The tube crimp has been used for placing the lot or control number (as provided for under 201.100(b)(6)) and for placing the expiration date for some products.

No known problems have been associated with such information appearing on the crimp of the dispensing tube and, therefore, this method is an acceptable way to comply with 201.17.

26. Several comments objected to the provisions in 201.17 that when single-dose containers are packed in individual cartons, the expiration date may properly appear on the carton only.

Several respondents noted that ampules are sometimes removed from the outer carton, particularly in hospitals, and that valuable information that is not a part of the immediate

container labeling is lost. The provision in this section regarding single-dose containers has been in effect for a number of years and was based on information that such an allowance was necessary for single-dose containers, primarily glass ampules, because of technical problems in labeling glass ampules on a batch-by-batch basis.

Some manufacturers are now placing expiration dates on single-dose containers; however, no information has been presented that expiration dating for all single-dose containers, particularly glass ampules, is feasible. Although the Commissioner recommends this activity, it was not his intent to propose revocation of the exemptions for single-dose containers as part of this revision of FDA regulations. Based on the few comments received which recommended additional revisions in this section, the Commissioner will not revoke these exemptions at this time, but will consider the recommendations for revisions for a future proposal.

27. Several comments recommended that for drugs which are also cosmetics (see also paragraph 42(h)) expiration dates should only be placed on the shipping carton and outer retail package because such products are typically purchased by the user with the outer retail package intact and the product is consumed in a relatively short period of time. The Commissioner advises that under the interim provisions of 211.137(f), most of these types of products will be exempted from the expiration dating requirements. But the so-called "drug-cosmetic" type of products are not free from stability problems; therefore, unless such products are stable for at least 3 years, expiration dating is required (see also paragraph 353 of this preamble).

IV. AMENDMENTS REGARDING DRUG LISTING AND ESTABLISHMENT REGISTRATION REQUIREMENTS FOR DRUG PRODUCT SALVAGING OPERATIONS

28. Several comments suggested that the word "human" be inserted between the words "licensed" and "biologicals" in 207.3(b) because veterinary biologicals are regulated by the U.S. Department of Agriculture. The Commissioner agrees with these comments and is amending the paragraph accordingly.

29. One comment recommended that the definition of "establishment" under 207.3(b) be broadened to include additional categories such as bulk sales by practitioners, antique shops, and dealers and trustees handling estate sales and/or bankruptcies. The Commissioner agrees that these are all examples of establishments that could engage in drug-salvaging operations, but believes that the proposed definition of "establishment" is preferred in order to provide coverage for any type of establishment that engages in drug product salvaging operations, including those identified in the comment.

30. Two comments suggested deletion of the word "may" in the phrase "may have been subjected to" improper storage conditions in the proposed 207.3(k) because the statement is too general and the requirement should only apply when the drug product has actually been exposed to adverse conditions. The Commissioner rejects this suggestion because it may not be possible in every instance to establish clearly the exact nature of the adverse circumstance to which a drug product has been exposed.

Therefore, in some instances, the salvager may only have sketchy information about improper storage conditions, such as unusual temperatures, and must assume that such conditions may have occurred in order to handle the salvaging operations properly.

31. Three comments concerned the proposed exemption of drug product salvagers from drug listing in 207.20. Two of the comments recommended that drug product lists be submitted prior to salvaging and one respondent recommended that a drug product list need not be submitted, but should be maintained by the salvager.

The Commissioner agrees that an inventory of drugs subjected to salvaging operations should be maintained, but does not agree that salvagers should submit a drug list under Part 207 (21 CFR Part 207). To clarify that an inventory of drugs involved in salvaging operations shall be maintained, provisions are added in 211.208 for maintenance of records for drug products subjected to salvaging operations.

32. One comment considered the registration requirement for a drug salvaging firm to be a waste of taxpayers' money and recommended that the recycling of any and all drugs and pharmaceuticals be prohibited. The Commissioner disagrees with this opinion. He does not agree that drug product salvaging should be prohibited where the integrity of the drug product is not compromised.

Otherwise costs to consumers might be increased. Individual firms are in a better position to determine the financial feasibility of a salvaging operation. The costs of registration, both to the Government (and the taxpayer) and to the registrant, are quite insignificant and probably less than the added costs that would result from the needless destruction of salvageable drug products.

V. LEGAL STATUS OF CGMP REGULATIONS

33. Several comments requested deletion of the word "drugs" in the title and insertion of the words "drug products" in order to be consistent with the title of Part 211 and the definition of 210.3(b)(4) and 210.1(a). Part 210 applies to all parts between Parts 211 and 229. Part 211 deals with finished dosage forms, but other parts may not. Therefore, the Commissioner finds that the more general term "drugs" applies better to the various types of drugs that are likely to be covered in Parts 211 to 229.

34. A number of comments objected, on diverse grounds, to use of the word "minimum" to describe the requirements in these regulations. Several respondents believed that current good manufacturing practice cannot be considered in terms of a "minimum" because that implies that firms adhering to the regulations are then merely at a threshold level of compliance. Other respondents suggested that "minimum" means that normal practices represent a higher standard and that there is an implication that the standards of these regulations fall below an acceptable level.

Some comments recommended that "minimum" not be used because no such reference to CGMP regulations is in the act. The Commissioner does not agree with these comments. The legislative history of the Drug Amendments of 1962 shows that section 501(a)(2)(B) of the act was included to raise the standards of drugs manufacturing by all manufacturers to the level of the current good manufacturing practice in the industry. Congress was quite concerned about the uneven and sometimes unacceptable quality of drug products from some portions of the pharmaceutical industry.

The purpose of section 501(a)(2)(B) of the act is to provide assurance that drug product quality would not fall below that which was feasible and available under contemporary technology. There is no implication that the standards

represented by these regulations are less than acceptable or below the industry's norm. On the other hand, there is no prohibition in the regulations against the manufacturing of drug products using better, more efficient, and innovative methods. In fact, the Commissioner encourages use of such methods because it benefits the consumer. Although the word "minimum" does not appear in section 501(a)(2)(B) of the act, its use is necessary in the CGMP regulations because of their binding legal nature (discussed in paragraph 35); that is, failure to meet the minimum standards of the regulation results in the product's being adulterated.

BINDING DRUG CGMP REGULATIONS

35. Several comments argued that 210.1 should be deleted because it is based on the erroneous proposition that CGMP regulations can be substantive. The comments urged that regulations issued under section 501(a)(2)(B) of the act are only interpretive. In support of their argument, many referred to the legislative history of the Drug Amendments of 1962. One commented stated the following:

Section 501(a)(2)(B) was enacted as part of the Drug Amendments of 1962, and, as reported by House Committee, those amendments would have included a provision empowering the FDA to issue GMP regulations under its formal section 701(e) rulemaking authority. (H.R. 11581, 87th Congress, Second Session.) The House Committee Report explained: "The promulgation of these regulations would be subject to opportunity for hearing and judicial review.

Thus, legal action could be brought against firms failing to abide by these standards and against the products they ship." (H.R. Rep. No. 2464, 87th Congress, Second Session, 2(1962).) The present form of section 501(a)(2)(B) was first enacted by the Senate.

The Senate Committee Report made clear that the provision was intended to authorize the FDA to issue "interpretative" regulations that would constitute only prima facie evidence of adulteration. (S. Rep. 1744, 87th Congress, Second Session, 9(1962).) In floor action on September 27, 1962, the House amended H.R. 11581 to be consistent with the Senate bill. (108 Congressional Record 19916 (daily edition 1962).)

Most of those relying on the legislative history argument quoted from the same Senate Committee Report. Other comments objecting to FDA's authority to issue binding CGMP regulations asserted that the four judicial decisions cited in the preamble to the February 13, 1976, proposal in fact did not support that authority. One comment reviewed the history of all four proceedings and concluded:

All of the cases cited by the Commissioner * * * recognize that the court cannot reach a conclusion contrary to Congressional intent. In those cases, there was no clear Congressional intent and the courts allowed the FDA to issue substantive regulations under section 701(a) of the Act. The legislative history with respect to the proposed CGMP regulations is crystal clear and does not permit the Commissioner to issue substantive regulations.

Because of the fervor reflected by these objections and because the Commissioner foresees identical objections being made to proposals to issue binding CGMP regulations for specific classes of drug products in the future, the Commissioner has decided that a lengthy exposition of the basis for his concluding that FDA has legal authority to promulgate such regulations is warranted.

The Commissioner intends that this statement will be definitive, and he does not contemplate reconsidering the issue of FDA's legal authority to issue substantive CGMP regulations in the future unless new materials, not discussed below, are brought to his attention. The question of whether a particular

regulation should be issued as binding or interpretive, of course, may always be raised, and comments on the wisdom of making these CGMP regulations binding are discussed in paragraph 36 below in this preamble.

With regard to the legislative history of the Drug Amendments of 1962, the Commissioner finds that none of the comments provided a complete or accurate picture of the enactment of the current section 501(a)(2)(B) of the act. Because of the emphasis placed by the persons objecting to "substantive" CGMP regulations on Congressional intent, the Commissioner believes a detailed review is necessary. On July 19, 1962, the Senate Judiciary Committee reported out S. 1552, the Senate version of what ultimately became the Drug Amendments of 1962. Section 5 of the July 19 bill would have amended section 501(a)(2) of the act to read as follows:

(2)(A) if it has been prepared, packed, or held under insanitary conditions whereby it may have been contaminated with filth, or whereby it may have been rendered injurious to health; or (B) if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packaging, or holding do not conform to 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.

The Secretary is authorized to issue interpretative regulations, upon notice and in accordance with the procedures set forth in section 4 of the Administrative Procedure Act (5 U.S.C. 1003), which shall, in any proceeding involving this paragraph, be prima facie evidence of what constitutes current good manufacturing practice.

The accompanying bill report (S. Rep. No. 1744, 87th Cong., 2d Sess. (July 19, 1962)), described this section at page 9, emphasizing that the "Secretary would be authorized to issue

interpretative regulations as to what constitutes current good manufacturing practice, and these regulations would be prima facie evidence in any proceeding under this section of the Food, Drug, and Cosmetic Act."

On August 3, 1962, President Kennedy submitted a series of amendments to the Senate Judiciary Committee. In response to this and to the public controversy then erupting over thalidomide, the Committee reconsidered S. 1552 and, on August 21, 1962, reported out a revised version of the bill.

One change was to reword section 5 of the bill so that section 501(a)(2) would be amended to read as follows:

(2)(A) if it has been prepared, packed, or held under insanitary conditions whereby it may have been contaminated with filth, or whereby it may have been rendered injurious to health; or (B) if it is a drug and 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.

The Judiciary Committee issued a second report to explain its proposed changes in S. 1552 (S. Rep. No. 1744, Pt. 2, 87th Cong., 2d Sess. (Aug. 21, 1962)). On pages 3 and 4, it discussed the revision of section 5 as follows:

The President, in the recommendations submitted for the consideration of the committee with his letter of August 3, 1962, proposed a revised version which included the following principal amendments to the reported bill: (1) It proposed to replace the provisions on regulations with prima facie evidentiary effect with a provision that the adequacy of the quality controls be determined "in accordance with regulations

promulgated by the Secretary on the basis of good manufacturing practice" after formal rulemaking procedures, i.e., after affording an opportunity for hearing, and for judicial review on the basis of the hearing record, with respect to such regulations.

* * * * *

The explanation accompanying the recommendations of the President expressed concern lest the language as to interpretative regulations with prima facie evidentiary effect invite endless de novo litigation on the question of what constitutes a good manufacturing practice each time there is enforcement action under the new quality control provisions.

The committee acceded to the President's request for elimination of the "prima facie" regulatory authority in the bill. It felt, however, on balance, that there was no need for inserting provisions for regulations through formal rulemaking on the subject of what is good manufacturing practice. Section 701(a) (21 U.S.C. 371(a)) now vests in the Secretary "authority to promulgate regulations for the efficient enforcement of this Act." This permits the Department to issue such regulations as it desires and their scope and effect will be the same as that of other regulations issued under such general authority.

Numerous regulations have been issued under section 701(a) and have been the subject of consideration and application in the courts in actions arising under the various provisions of the act not now subject to formal rulemaking procedures.

During the floor debate on S. 1552 on August 23, Senator Eastland, Chairman of the Judiciary Committee, elaborated on the meaning of section 501(a)(2) as it would be amended by the bill:

Section 5, as it would read under the August 20 amendments, is designed to assure that drugs are manufactured according to good manufacturing practice. It would deem a drug to be adulterated and thus subject to seizure if made under facilities, methods, or controls that are inadequate to assure that the drug meets the specifications of a quality product. Adulteration could also be found if such facilities, methods, or controls were not operated or administered in conformity with good manufacturing practice.

Since the competitive position of responsible manufacturers depends in large part on the confidence of the medical profession and the public, it will be in their own interest to maintain high standards of current good manufacturing practice which will provide a readily determinable basis for enforcement proceedings against any substandard operator.

The Secretary could use his general rulemaking authority under section 701(a) of the act to announce what he, in the administration of the act, considers to be good manufacturing practice insofar as methods, facilities, controls, and their operation and administration are concerned. As in the case of other regulations, the court in the final analysis will pass upon the scope and effect of such regulations. (108 Cong. Rec. 16303-4 (Aug. 23, 1962).)

Senator Kefauver concurred in this change, stating, "This provision has been strengthened considerably in comparison to the bill which was reported in July." (Id., at 16306-7). The Commissioner thus concludes that when it unanimously approved S. 1552 on August 23, 1962, the Senate obviously believed that the problem identified by the President--"endless de novo litigation * * * each time there is enforcement action"--had been resolved.

The Senate must, therefore, have intended that regulations issued under section 501(a)(2)(B) of the act be more than merely prima facie evidence of what constitutes current good

manufacturing practice, i.e., that they be given at least the same force as any other regulation issued under section 701(a) of the act. He also finds that the statement relied upon by most comments as proof that only interpretive regulations could be issued appeared in the first Senate Report and was explicitly reversed in the second Senate Report.

One month later, the House Interstate and Foreign Commerce Committee reported out H.R. 11581, the House bill that preceded the Drug Amendments of 1962. (H.R. Rep. No. 2464, 87th Cong., 2d Sess. (1962)). Section 101(a) of this bill proposed to amend section 501(a)(2) of the act to read as follows:

(2)(A) if it has been prepared, packed, or held under unsanitary conditions whereby it may have been contaminated with filth, or whereby it may have been rendered injurious to health; or (B) if it is a drug and 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 (as determined in accordance with regulations promulgated by the Secretary) 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 addition, paragraph (b) of section 101 would have amended section 701(e) of the act to provide that regulations under section 501(a) would be issued by formal rulemaking procedures (rather than the informal procedures under section 701(a) of the act). The Committee Report accompanying H.R. 11581 explained this provision as follows (H. Rep. 2464, 87th Cong., 2d Sess. 2 (Sept. 22, 1962)):

Section 101 of the reported bill would amend section 501(a)(1) [sic] of the Federal Food, Drug, and Cosmetic Act to deem a drug to be adulterated if the methods, facilities, or controls

used in its manufacture, processing, packaging, or holding fail to conform to, or are not operated or administered in conformity with, good manufacturing practices as determined in accordance with regulations to be issued by the Secretary of Health, Education, and Welfare which are designed to assure that the drug is safe and has the identity and strength and meets the quality and purity characteristics which it purports or is represented to possess * * * The promulgation of these regulations would be subject to opportunity for hearing and judicial review. Thus, legal action could be brought against firms failing to abide by these standards and against the products they ship.

The House of Representatives debated H.R. 11581 on September 27, 1962. Congressman Schenck offered several amendments that day, one of which would delete the parenthetical element in section 101(a), and all of section 101(b), from the bill. He explained this amendment as follows:

My amendment to section 101 of the bill, which was approved by the committee, provides simply that the drug will deem[sic: be deemed] to be adulterated and subject to seizure if the methods, facilities, or controls used in the manufacture of the drug do not conform with current good manufacturing practice, as determined in accordance with regulations promulgated by the Secretary.

The purpose of this provision is to enable the Secretary to require all companies producing drugs to observe the high standards that are now followed by the better manufacturers. It is intended that the Secretary's regulations will define minimum standards of good manufacturing practice, rather than setting forth an exclusive method by which some particular drug product may be made. Manufacturers whose methods, facilities, and controls exceed the minimum standards will not be required to lower their own standards, so long as they can show that their own practices meet or exceed these minimum requirements.

The principal purpose of the provision is to assure that the same high manufacturing standards are followed in making so-called old drugs that the law now requires in the making of so-called new drugs. Before any manufacturer is permitted to make a new drug he must file complete details of his manufacturing process with the Food and Drug Administration. It is not intended that the regulations issued under section 101 will apply to the manufacturer of new drugs insofar as the methods, facilities, or controls used in making these new drugs but that the Food and Drug Administration will require that such drugs meet the requirement of this act as to safety, and has the identity and meets the quality and purity characteristics which it purports or is represented to possess. The committee adopted an amendment which would make the formal rulemaking procedures of section 701(e) of the Federal Food, Drug, and Cosmetic Act applicable to regulations referred to which may be made pursuant to the above amendment. I am opposed to the amendment in section 101(b) of the bill which would require the Secretary to hold a formal hearing under section 701(e) of the Federal Food, Drug, and Cosmetic Act in order to issue regulations as to what constitutes 'current good manufacturing practice.' I favor the approach adopted by the Senate under which this determination is made pursuant to section 701(a) of the act.

This procedure permits the Secretary to issue such regulations as he desires and their scope and effect will be the same as that of other regulations, issued under such general authority. This procedure is more flexible. Numerous regulations have been issued under this section and they have been the subject of consideration and application in the courts in actions arising under the various provisions of the act not now subject to formal rulemaking procedures. (108 Cong. Rec. 19895-6 (Sept. 27, 1962).)

The Schenck amendment was concurred in by Congressman Harris, Chairman of the House Commerce Committee, who observed that the amendment "is taken, in part, from the

Senate bill, S. 1552 * * * The gentleman from Ohio [Mr. Schenck] has advised me of the need not to tie this provision in with section 701(e) * * *" 108 Cong. Rec. 19916 (Sept. 27, 1962). The amendment was agreed to and, as approved by the House of Representatives, the legislation would amend section 501(a)(2) to read:

(2)(A) if it has been prepared, packed, or held under unsanitary conditions whereby it may have been contaminated with filth, or whereby it may have been rendered injurious to health; or (B) if it is a drug and 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.

The Commissioner finds from this history that the House of Representatives believed that CGMP regulations would have the same legal status as other FDA regulations, and moved to revise language to conform to S. 1552, as passed, solely to eliminate the requirement that CGMP regulations be issued pursuant to the formal rulemaking procedures of section 701(e) of the act. Because there was no difference between the House and Senate bills insofar as the amendment of section 501(a)(2) of the act was concerned, it was not a subject of the Conference Report (H. Rep. No. 2526, 87th Cong. 2d Sess. (Oct. 3, 1962)), nor was it modified or debated further by either the Senate or the House when each voted to approve the Drug Amendments of 1962 (on October 3 and 4, 1962, respectively).

Based on this complete review of the legislative history of section 501(a)(2)(B) of the act, the Commissioner concludes that there is no support for the proposition that Congress intended that CGMP regulations should be merely interpretive.

At the least, Congress wanted CGMP regulations to have the same force and effect as other regulations issued under section 701(a) of the act. (See the second Senate Report and Rep. Schenck's description of his amendment, above). To the extent that a stronger Congressional mandate can be gleaned from the various reports, amendments, and debates, it appears that binding standards were to be issued by FDA and issued through the less cumbersome notice-and-comment rule making procedures of section 701(a) of the act rather than the more complex section 701(e) mechanism.

Therefore, the Commissioner rejects the argument that 210.1 exceeds the authority conferred by Congress under sections 501(a)(2)(B) and 701(a) of the act. With respect to judicial interpretations of FDA's authority to issue substantive rules, the Commissioner believes that the cases cited in the February 13, 1976 preamble and decisions handed down since February 13, 1976 are directly relevant to, and further support, his conclusion that CGMP regulations can be issued as binding standards. In 1973, the Supreme Court reviewed the legality of two interrelated FDA regulations.

One, now codified in 21 CFR 314.111(a)(5), set forth in detail the scientific principles that the Commissioner believed are part of the requirement in section 505(d) of the act that the effectiveness of a drug be demonstrated by "substantial evidence consisting of adequate and well-controlled studies." The second regulation, now codified in 21 CFR 314.200, contained standards for FDA to determine whether a request for a hearing on the denial or withdrawal of approval of a new drug application (NDA) presented a genuine and substantial issue of fact. At stake in the case of *Weinberger v. Hynson, Westcott and Dunning, Inc.*, 412 U.S. 609(1973), was whether an applicant was entitled to a full evidentiary hearing on the approvability of its product, and at such a hearing could offer whatever evidence it felt met the statutory standards of effectiveness, or whether FDA could summarily deny or withdraw approval of the NDA because the agency found that

the applicant's evidence did not meet the standards in the regulations for evidence of effectiveness.

Manufacturers contended that FDA's regulations could not serve as the basis for denying them a full evidentiary hearing under section 505 of the act. The agency believed that the regulations were a reasonable method of screening out unnecessary hearings and thereby managing an otherwise overwhelming workload. The Supreme Court concluded that both of the regulations were within the authority of the Commissioner under section 701(a) of the act and therefore FDA could act on NDA's without a full hearing where evidence failed to satisfy the FDA regulations. It said (*id.* at 622):

The standard of 'well-controlled investigations' particularized by the Regulations is a protective measure designed to ferret out those drugs for which there is no affirmative, reliable evidence of effectiveness. The drug manufacturers have full and precise notice of the evidence they must present to sustain their NDA's, and under these circumstances we find the FDA hearing regulations unexceptionable on any statutory or constitutional ground.

The Supreme Court, in this and related cases, discussed FDA's authority to determine whether a drug was a "new drug" under section 201(p) of the act (and thus subject to the requirements of section 505 of the act). It described favorably the review of over-the-counter (OTC) drugs under the procedures set forth in 21 CFR 330.10, by which OTC drugs are being classified as "new" or "generally recognized as safe and effective and not misbranded," the latter not subject to the new drug provisions of the act. These procedures were also promulgated under the authority of section 701(a) of the act. The Court stated, in *Weinberger v. Bentex Pharmaceuticals, Inc.*, 412 U.S. 645, 653 (1973) that:

We think that it is implicit in the regulatory scheme, not spelled out in *haec verba*, that FDA has jurisdiction to decide

with administrative finality, subject to the types of judicial review provided, the 'new drug' status of individual drugs or classes of drugs. The deluge of litigation that would follow if 'me-too' drugs and OTC drugs had to receive de novo hearings in the courts would inure to the interests of manufacturers and merchants in drugs, but not to the interests of the public that Congress was anxious to protect by the 1962 amendments, as well as OTC drugs and drugs covered by the 1972 (Drug Listing) Act. We are told that FDA is incapable of handling a caseload of more than perhaps 10 or 15 de novo judicial proceedings in a year. Clearly, if FDA were required to litigate, on a case-by-case basis, the 'new drug' status of each drug now marketed, the regulatory scheme of the act would be severely undermined, if not totally destroyed. Moreover, a case-by-case approach is inherently unfair because it requires compliance by one manufacturer while his competitors marketing similar drugs remain free to violate the Act * * *.

In a third case decided at the same time, *Ciba Corp. v. Weinberger*, 412 U.S. 640 (1973), the Court said (*id.* at 643-4) that "the definition of new drug as used in section 201(p)(1) involves a determination of technical and scientific questions by experts. The agency is therefore appropriately the arm of Government to make the threshold determination of the issue of coverage * * *." The Commissioner notes that even prior to these rulings, most major manufacturers of OTC drugs had recognized the reasonableness as well as legal propriety of the OTC review as a mechanism within the authority of section 701(a) of the act to classify drugs as "new" or "not new." Indeed, for over 5 years now, these firms have been participating in this review, and the Commissioner expresses his gratitude for this cooperation. Subsequent to these rulings by the highest Federal court, another case arose over the issue of whether FDA could promulgate regulations under section 701(a) of the act that represented binding rules relating to prescription drugs under section 503(b) of the act. The specific issue was whether FDA could, by regulation, declare products

containing more than certain amounts of vitamin A or D to be prescription drugs. The opponents of the regulation, in an interesting parallel to the comments on the CGMP regulations, argued that only regulations issuable under section 701(e) of the act procedures could be binding and that the legislative history of section 503(b) of the act demonstrates that FDA could issue only interpretive regulations. The United States Court of Appeals for the Second Circuit rejected these contentions in *National Nutritional Foods Ass'n. v. Weinberger*, 512 F.2d 688 (1975). It stated:

We have come to recognize that, if the administrative process is to be practicably effective, specific regulations promulgated pursuant to general statutory delegation of authority must be treated as authoritative, whether labeled "substantive" or "interpretive," especially in areas where the agency possesses expertise not shared by the courts. In the event its views are unlikely to be distributed by the court in an enforcement proceeding * * *. Whatever doubts might have been entertained regarding the FDA's power under 701(a) to promulgate binding regulations were dispelled by the Supreme Court's recent decision in *Weinberger v. Hynson, Westcott, & Dunning* * * * and its companion cases * * *. (id. at 696).

Surely an agency which possess the power to determine administratively what products are "new drugs" has the authority to decide what products are "prescription drugs". (id. at 699).

The decisions in the *National Nutritional Foods*, *Hynson, Bentex*, and *Ciba* were cited by the Commissioner because he believes that they conclusively rule that regulations issued under section 701(a) of the act are binding and that the justifications for issuing substantive regulations in other areas are directly applicable to CGMP regulations. Similar to the Court's observations in *Hynson* quoted above, the statutory standard of "current good manufacturing regulations" can and should be particularized as a protective measure to identify

those manufacturing practices which are at a minimum necessary to assure drug quality. The drug manufacturers have full and precise notice of the CGMP requirements they must fulfill to sustain the acceptability of their products under section 501(a)(2)(B) of the act, as the Commissioner noted in the February 13, 1976, preamble.

Substantive regulations also provide greater certainty about the agency's expectations because, in promulgating such regulations, the agency must carefully distinguish standards it seriously intends to enforce from those it finds desirable but not essential. The Commissioner also stated in the 1976 proposal that binding CGMP regulations would assist courts and expedite enforcement proceeding under the act. As with "new drug" determinations discussed in *Bentex*, if each CGMP requirement has to receive a de novo hearing in each and every enforcement proceeding, the burden of litigation that would result would not be in the public interest, nor would it be equitable to competing manufacturers who were not involved in such litigation.

President Kennedy and the second Senate Report made the same arguments in deleting the reference to interpretive regulations from S. 1552. The agency has avoided this problem over the last several years because agency priorities have been concentrated in areas other than drug CGMP enforcement; it is not anticipated that this allocation of resources will continue indefinitely and, with the issuance of these regulations, more regulatory proceedings are probable. In *Ciba*, the Court noted the technical and scientific expertise appropriate for at least the threshold determination of "new drug" status.

The Commissioner believes that determination of what is the "current good manufacturing practice" in the drug industry also requires technical and scientific expertise, as well as a unique ability to observe the entire industry. These CGMP regulations were developed with the participation of pharmaceutical

chemists employed by FDA, individuals qualified by formal training as well as by valuable experience in reviewing the good (and bad) current (and past) production and control techniques set forth in original NDA's and abbreviated NDA's, supplemental applications, antibiotic certification forms, biological establishment and product licenses, new animal drug applications, and proposed and final compendial standards.

In addition, FDA investigators who conduct and/or review inspections of manufacturers under the act also participated in preparing this document. Although, as one comment noted, FDA does not manufacture drugs, it does not follow that FDA cannot determine current good manufacturing practice for drugs. On the contrary, FDA may be uniquely able to do so, because it and it alone has had access to the facilities and records of every manufacturer of pharmaceuticals in this country.

Given the fact that many production and control processes are considered by individual firms to be trade secrets, it is unlikely that competitors or independent private third parties such as compendial authorities have the same ability as FDA to discover what non-public practices other than their own are current and which of these are good. Subsequent to the February 1976 proposal, other courts have considered and affirmed FDA's authority to promulgate binding of substantive regulations pursuant to section 701(a) of the act. See, e.g., *Cosmetic, Toiletry and Fragrance Association v. Schmidt*, 409 F. Supp. 57 (D.D.C., Feb. 3, 1966), appeal docketed No. 76-1242 (D.C. Cir., Feb. 5, 1976)(regulation requiring warning labels on aerosolized products, issued under sections 201(n), 602(a), and 701(a) of the act, upheld; *American Frozen Food Institute v. Mathews*, 413 F. Supp. 548 (D.D.C. March 30, 1976), aff'd sub nom. *American Frozen Food Institute v. Califano*, 555 F.2d 1059 (D.C. Cir. May 12, 1977)(regulations establishing common and usual names for nonstandardized foods, issued under sections 403(i) and

701(a) of the act, upheld); National Confectioners Ass'n. v. Mathews, CCH Food, Drug & Cos. L. Rep. 38,062 (D.D.C. April 14, 1976), aff'd sub nom. National Confectioners Ass'n v. Califano, Docket No. 76-1617 (D.C. Cir. Jan. 20, 1978)(CGMP regulations for cocoa products and confectionery relating to lot coding on finished product packages and shipping containers and to distribution records of lots, issued under sections 502(a)(4) and 701(a) of the act, upheld); Federation of Homemakers v. Schmidt, 385 F. Supp. 362(D.D.C. 1974), aff'd 539 F.2d 740 (D.C. Cir. June 10, 1976)(regulation establishing requirements for "imitation" foods, issued under sections 403(c) and 701(a) of the act, upheld); Almay, Inc. v. Weinberger, 417 F. Supp. 758 (D.D.C. June 30, 1976), rev'd on the grounds, No. 76-1718 (D.C. Cir. Dec. 21, 1977) authority to issue regulations regarding labeling and supporting evidence of cosmetics claiming to be "hypoallergenic," under sections 301(b), 602(a) and (b) and 701(a) of the act upheld); United States v. Nova Scotia Food Prod. Corp., 417 F. Supp. 1364 (E.D.N.Y., Aug. 17, 1976), rev'd on the grounds, No. 76-6169 (2d Cir. Dec. 15, 1977)(CGMP regulations regarding brining and heating of fish in the production of smoked fish may be promulgated under sections 402(a)(4) and 701(a) of the act).

The Commissioner notes that two of the cases dealt specifically with the validity of CGMP regulations issued under the statutory standards relating to adulterated foods, which do not explicitly refer to "current good manufacturing practice."

It would indeed be anomalous that those regulations could be issued as legally binding if regulations amplifying section 501(a)(2)(B) could not be. The Commissioner interprets much of the concern over FDA's authority to issue binding regulations as reflecting a belief that the CGMP regulations can be arbitrary, need not be based upon actual current practice, and may exceed what is necessarily "good" for drug quality.

There also seems to be a belief that binding regulations cannot be changed and are beyond review by the courts. These perceptions are in error. The Administrative Procedure Act clearly provides that regulations which are arbitrary or capricious may be overturned by a reviewing court. 5 U.S.C. 706. The legislative history of section 501(a)(2)(B) of the act and cases involving enforcement of CGMP regulations, e.g., United States v. An Article of Drug * * * "White Quadriseet", 484 F.2d 748 (7th Cir. 1973)) established that the regulations must be based on current industry practice, although not necessarily on the predominant practice in the industry.

The agency is directed to consider the current "good" practices. In determining current practice, the agency has relied upon the knowledge and expertise of FDA staff developed from the review of NDA's and ANDA's, antibiotic certification forms, biological licenses, and compendial standards submitted to the agency, and from establishment inspections made during the last half decade. A "good" practice was included in these regulations only if it is feasible for manufacturers to implement the practice, if the practice contributes to assuring the safety, quality, and purity of the drug product, and if the value of the contribution or added assurance exceeds the cost, in terms of dollars and/or other burdens, of implementing or continuing the practice.

The Commissioner does not believe it is legally required that, in addition to reliance upon agency expertise, he must include in the record specific examples of each practice mentioned in these regulations. Regarding judicial review of regulations, the Commissioner notes that such review is assured by the Administrative Procedure Act whether the regulations are deemed interpretive or substantive. Judicial review is available in any enforcement proceeding brought against a particular manufacturer or product. Pre-enforcement review is also available. *Abbott Laboratories v. Gardner*, 387 U.S. 136 (1976). Thus, the Commissioner believes that the fears that

substantive, binding CGMP regulations somehow deprive individuals of legal protections are unfounded.

As noted at the outset of this discussion, the Commissioner does not intend in the future to reconsider the legal authority of FDA to promulgate binding CGMP regulations under section 701(a) of the act, unless new material, not discussed above, is presented to him that raises substantial doubt as to the correctness of the analyses and conclusions he set forth above. For reasons discussed in this paragraph and in paragraph 36 below, the Commissioner has also decided that these CGMP regulations shall be issued as binding. The Commissioner advises that any person who still questions FDA's authority to do this is welcome to seek prompt pre-enforcement judicial review of this authority.

36. A number of comments suggested, in effect, that whether or not FDA could lawfully issue "binding" CGMP regulations, it would be unwise for the agency to do so. These individuals cited the complexity and variability of manufacturing control processes, emphasizing the variety of options available and the need for freedom of choice among these options by various manufacturers depending on cost and technological factors. They further complained that FDA lacked the expertise to determine which practices were best and that, by "freezing-in" techniques, FDA would discourage innovation and development of new procedures which might increase the assurance of product quality.

The comments objected to the presumption that would follow from a technical violation of the CGMP regulations that the product was therefore adulterated and that individuals, under the legal doctrine of strict criminal liability under the Federal Food, Drug, and Cosmetic Act, were criminally responsible for these violations. Binding regulations would, in their opinion, provide the agency no flexibility for discretion in enforcement of the act.

Finally, the comments objected that there was no need for binding regulations because there were only a few large pharmaceutical manufacturers involved in production of most drugs; because these were subject to frequent inspections by FDA; and because in the past, these firms had been subject to few problems, few recalls, and rare legal proceedings. This history suggested that most firms were in substantial compliance with the regulations regardless of whether they were classified as substantive or interpretive.

The Commissioner has evaluated these objections and found that, although some have merit, none is so serious as to outweigh the benefits from making CGMP regulations binding. Recognizing the diversity of manufacturing and control procedures, the Commissioner has endeavored wherever possible to state CGMP regulations in the terms of objectives to be attained, rather than methods of attaining such objectives. Procedures have been specified only where essential to assure product quality under the act.

Thus, these regulations provide flexibility to manufacturers to select the methods and processes that will be most suitable to the products and operations of the individual firms. This flexibility should also permit the development of novel approaches to attaining the same objectives. In those few cases where precise procedures are set forth in these regulations, individuals who believe that alternative mechanisms may also be acceptable are invited to petition the Commissioner to amend the specific regulation to permit such alternatives.

As discussed in paragraph 35 of this preamble, the Commissioner does not believe that FDA lacks sufficient expertise to develop and promulgate CGMP regulations and advises that the public procedures for commenting on these proposed CGMP regulations, together with the opportunity to petition the agency for changes in the regulations, provide individual manufacturers with an opportunity to correct any

errors in FDA's information. Thus, the Commissioner does not believe the agency lacks sufficient information to justify making CGMP regulations binding rather than interpretive.

With regard to the alleged lack of flexibility in the enforcement of "binding" CGMP regulations, the Commissioner believes that the comments have confused the question of whether a violation exists with the question of whether FDA will take action upon the violation.

In numerous areas, FDA has established tolerances for actionable offenses and is currently in the process of establishing regulations setting forth agency policy with regard to prosecutions for violations of the act. It should be noted, however, that even in the absence of any CGMP regulations, whether binding or not, the doing of or failure to do any particular act which is inconsistent with current good manufacturing practice results in the product being legally adulterated, even if no legal action is brought. That is to say, the existence of CGMP regulations does not create violations of the law where they did not previously occur. The question rather is whether the violator will be prosecuted or enjoined and/or the product seized, an issue beyond the scope of this rule making.

Finally, with regard to the objection that there is no need to make these regulations binding since most major pharmaceutical manufacturers are in substantial compliance with the current regulations, the Commissioner believes that this is simply not relevant to the question of whether CGMP regulations should be binding or interpretive. The most significant justification for having the regulations binding is to minimize the burden on the government and on the courts in a case where a violation does occur.

When the regulations are merely interpretive, the agency must provide expert testimony in each trial to demonstrate what the current good manufacturing practice in the industry is,

notwithstanding the regulation. The cost of locating and preparing such expert witnesses and bringing them to the trial, as well as the judicial time taken in hearing these witnesses, would be eliminated by having binding regulations.

In the event that a challenge is raised about the validity of the regulation, FDA can present to the court the administrative record underlying the regulation in lieu of any expert testimony. Thus, it is not the proportion of manufacturers who are in compliance with the regulations but the number who are out of compliance and whose noncompliance justifies regulatory action that necessitates making these regulations binding.

For these reasons the Commissioner has concluded that insofar as he has discretion to issue CGMP regulations as either binding or interpretive, he elects to make them binding.

37. Several comments suggested the words "where applicable" be inserted in the first sentence of 210.1(a). The comments argued that, as proposed, conformance to every requirement regardless of the need to do so. The Commissioner concludes that there are numerous examples of flexibility built into the CGMP regulations. Words like "appropriate" and "as necessary" are used in the regulations to make it clear that requirements which are not relevant to a given manufacturer's operation do not apply. In addition, a new paragraph (b) is established in 210.2 to clarify that the requirements apply only to those operations subject to the CGMP regulations in which the manufacturer is engaged.

38. Two comments recommended that the references in this section be Parts 210 through 226 instead of Parts 210 through 229, since 229.25 was being revoked. Since the Commissioner has reserved all parts between 210 and 229 for current good manufacturing practice regulations, the reference is appropriate. Even though 229.25 has been revoked, Part 229 may be used in the future.

39. One comment suggested insertion of the phrase "and testing and quality control thereof" after the words "the manufacture, processing, packing, or holding of a drug product" in 210.1(d). Because "manufacture, processing, packing, or holding of a drug product" is defined in 210.3(b)(12) to include testing and quality control of drug products, the Commissioner rejects this comment.

40. A large number of comments recommended that the personal liability statement in 210.1(b) be eliminated. Some comments suggested that an individual should be held responsible only if actual contamination has occurred. Others recommended modifying the liability statement by requiring willful and knowing intent to violate the law. One comment said this was unclear as to who was covered by the section and that it was not useful in clarifying the requirements of the act.

Another asked about the definition of "responsible." The Commissioner notes that actual contamination of a drug does not have to occur for the article to be deemed adulterated under section 501 (a)(2)(B) of the act. Further, the act does not require a showing of intent for a person to be held accountable under the act. *United States v. Dotterweich*, 320 U.S. 277, (1943); *United States v. Park*, 421 U.S. 658 (1975).

It would be contrary to public policy and congressional intent, as well as beyond the Commissioner's authority, to require the showing of actual contamination or intent. Congress purposely did not do so in order to provide the maximum protection of the public health. With regard to clarifying "person," the Commissioner advises that the word "person" is defined in section 201(e) of the act to include corporations and partnerships as well as individuals. Under section 301(d) of the act, the adulteration of any drug is a prohibited act, and under section 303(a) "any person who violates a provision of section 301" is subject to criminal penalties. Thus, the reference to "the person" in 210.1(b) merely parallels the statutory language.

The reference to the word "responsible" is in accord with interpretations of the act by the Supreme Court of the United States. See *United States v. Park*, 421 U.S. 658 (1975). Thus, the Commissioner does not believe that this language is unclear or misleading. He also believes that, although 210.1(b) is not essential to the regulations and merely reflects the legal position of the agency, it is a useful exposition of FDA policy with regard to failure to comply with the CGMP regulations. For this reason, the language is retained in the final order. 41. One comment said the CGMP regulations, as proposed, set up FDA as both prosecutor and judge and deprive persons of due process.

The Commissioner finds that penalties for violation of these regulations (i.e., seizure of violative products, injunctive sanctions, and criminal prosecution) are imposed by judicial proceedings in United States courts, where the U.S. Department of Justice serves as prosecutor, Federal judges preside, and in criminal cases there is a right to trial by jury.

The role of FDA is twofold: First, it establishes standards amplifying the statutory language (through issuance of CGMP regulations after public comment); and second, it investigates to determine whether these standards have been violated. Affected persons have full legal rights, including the right to challenge the regulations as being beyond the authority of the act. The Commissioner finds no rationale to suggest these CGMP regulations compromise any person's right to due process.

VI. APPLICABILITY OF CGMP REGULATIONS; EXEMPTIONS

42. Many comments said there should be exemptions or waivers from the CGMP regulations for certain classes of drugs or specialized kinds of manufacturing activities. These comments came from manufacturers of bulk drugs, veterinary drug products, radiopharmaceutical drug products, biological drug products, so-called "drug-cosmetic" products, and wholesalers and retail dispensers of drug products.

These comments, except one, asserted that the CGMP regulations were inappropriate, unnecessary, excessive, or not part of current industry practice when applied to the type of product identified; the exception (discussed in paragraph g. below), together with one comment regarding a particular product line, questioned FDA's legal authority to apply CGMP regulations to certain types of businesses or products.

As discussed in the preamble to the February 13, 1976 proposal, the Commissioner intends to propose at future times CGMP regulations for specific classes of drug products such as small volume parenterals, compressed medical gases, and radiopharmaceuticals. (See, e.g., the proposal regarding LVP's published in the FEDERAL REGISTER of June 1, 1976 (41 FR 22202).)

In addition, regulations for certain kinds of manufacturing activities such as manufacturing of bulk drug components, repacking, or relabeling will be proposed. Generally, these future regulations will supplement, and in some situations supersede, the more general CGMP regulations.

As these proposals are issued, the need for waivers from or modifications in the general CGMP regulations should be diminished. After considering these plans and the comments regarding exemptions for specialized drug products or manufacturing activities, the Commissioner has reached the

following conclusions: a. Bulk drugs. It is first necessary to distinguish between (1) "drug products" (i.e., finished dosage forms) that may be held in bulk containers, and (2) bulk drug "components" (i.e., ingredients intended for use in the manufacture or processing of a drug product).

The CGMP requirements set forth in Part 211 are intended to apply to the preparation of a finished dosage form, whether or not in packaged form. This is clearly set forth in the regulations (210.3(b)(4) and 211.1(a)). Although these CGMP regulations are not applied to the manufacture of bulk drug components, there are numerous instances where good manufacturing practices for bulk drug components would parallel the requirements set forth in Part 211.

For this reason, FDA will utilize the standards of Part 211 as guidelines during inspections of manufacturers of bulk drug components under the jurisdiction of the act. b. Veterinary drug products. Veterinary drug products shall continue to be subject to the general CGMP regulations for all drug products, with certain specific exceptions, namely 211.42(d), 211.46 (d), and 211.72. Comments regarding the appropriateness of individual provisions of these regulations to veterinary drug products have been considered and responded to under the sections involved.

When the provisions of a section in the regulations do not apply to veterinary drug products, exemptions for such products are stated in that section. c. Radiopharmaceutical drug products. The general CGMP regulations are suitable requirements for the preparation of radiopharmaceutical drug products.

When the Commissioner was aware of situations where the requirements are not appropriate, exemptions were made from these final regulations. Supplemental requirements specific for radiopharmaceuticals will be proposed in the future. d. Biological drug products. The Commissioner notes that section

902(c) of the act parallels section 351(g) of the Public Health Service Act (42 U.S.C. 262(g)), which provides that section 351 does not affect, modify, repeal, or supersede the Federal Food, Drug, and Cosmetic Act.

The agency has consistently interpreted these provisions to be additive; that is, although they preclude duplicative or inconsistent regulation under the two acts, where one statute speaks to a matter regarding biological products and the other statute is silent, the express statutory provisions govern, regardless of the statute in which they appear. Thus, for example, the provisions of section 505(i) of the act regarding investigational use of new drugs have been consistently held to apply to biological products because no part of section 351 of the Public Health Service Act addresses investigational use of biologics (21 CFR 312.1(g)). Because section 351 of the Public Health Service Act does not refer to current good manufacturing practice and because biological products are considered to be drugs subject to section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act, the Commissioner believes it is consistent with both laws to apply current good manufacturing practices to biological drug products.

Biological products are now manufactured according to current good manufacturing practice and regulated under parts 600 through 680 (21 CFR parts 600 through 680), in particular the establishment license and product license provisions. Sections 210.2 and 211.1 clearly provide that the more specific biologic regulations prescribed in 21 CFR Parts 600 through 680 will supplement or supersede, where appropriate, the more general drug CGMP regulations.

The Commissioner believes it possible that provisions in the general CGMP regulations may be inappropriate for certain biological products and would make appropriate changes to assure that the CGMP requirements would not increase manufacturing costs without a commensurate increase in safety, purity, potency, or efficacy. However, no specific

examples were submitted to FDA in response to the proposal that can be considered as areas for exempting biological drug products.

The Commissioner invites interested persons to submit petitions under 10.30 to amend particular provisions of the CGMP regulations to account for the special technologies or incompatibilities of biologics. e. Compressed medical gases. The agency will propose specific CGMP regulations for compressed medical gases. Until such regulations can be proposed for public comment, comments received and evaluated, and a final regulation published, however, the Commissioner concludes that the requirements in the more general CGMP regulations, with certain stated exceptions, are applicable.

It would not be in the public interest to delay a final regulation based on the February 13, 1976 proposal until FDA can promulgate specific CGMP regulations for compressed medical gases. f. Repackaging and relabeling. Only certain portions of the general CGMP regulations apply to repackaging and relabeling operations. For example, the requirements pertaining to labeling control apply to repackers and relabelers, while the requirements for compounding a drug product do not apply since repackers/relabelers do not compound drug products. The CGMP regulations apply to repackaging and relabeling operations at locations that are different from the place of manufacture. Supplemental CGMP regulations regarding this unique type of drug processing will be proposed in the future. g. Wholesalers. Section 501(a)(2)(B) of the act provides that a drug shall be deemed 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 current good manufacturing practice * * *."

This section, through the operation of section 301(k) of the act, applies to wholesalers, retailers, pharmacies, and hospitals, as well as to manufacturers. However, the CGMP

regulations set forth in part 211 apply only to establishments engaged in the preparation of a drug product. Therefore, these regulations do not apply to the wholesalers, retailers, pharmacies, and hospitals engaged in activities that are traditional to those establishments. The wholesaler, however, is a particularly important link in the distribution chain between manufacturer, retailer, and consumer.

The Commissioner encourages wholesalers to adopt applicable provisions of the CGMP regulations to insure that drug products are handled and stored in a manner that will not contribute to loss of identity, strength, quality and purity. In addition, they are responsible for being able to identify the distribution of drug products that are subject to recall or market withdrawals. Recall strategy will frequently involve wholesalers as consignees and intermediate distributors when recalls are to the retail or consumer levels. In the FEDERAL REGISTER of June 16, 1978 (43 FR 26202), FDA published regulations to provide guidance to manufacturers and distributors in this area.

It is especially important for wholesalers to maintain adequate records to assure effective recall or market withdrawal. If future experience indicates to FDA that recalls and market withdrawals are being adversely affected by inadequate recordkeeping on the part of the wholesalers, the Commissioner will give further consideration to the need for specific CGMP regulations for wholesalers. h. Drugs that are also cosmetics. A number of comments, including a petition to the Commissioner, were received regarding the applicability of the proposed general CGMP regulations to a class of products identified as "cosmetic-drug products" and described as those which: (1) Meet the definitions of both "drug" and "cosmetic" under section 201 of the act; (2) represent a minimal health or safety risk; and (3) are marketed over-the-counter for regular and frequent consumer use without dosage limitations. Examples of these products were described as medicated skin

creams, anti-bacterial soap, antiperspirants, and topical sunburn prevention products.

Specifically, the comments requested separate CGMP regulations for this alleged class of drugs, and one comment submitted a proposed new part 213 for drug-cosmetic products, drafted in the style and format of other CGMP regulations for drugs. Another comment recommended that, because the drug-cosmetic products were so similar to related cosmetic products, CGMP regulations for those two classes of products be proposed and adopted together, separate from those relating to drug products generally.

The Commissioner has concluded that these regulations, except expiration dating for certain human OTC drug products described in paragraph 353 of this preamble, must apply to all products meeting the definition of drug products, whether the drug products are highly potent prescription drugs or are OTC drugs of the type described as "cosmetic-type." Past experience of the agency has demonstrated that the public has been put in a hazardous situation because of manufacturing errors in OTC products, such as by the substitution of spirits of camphor for castor oil.

Further, the Commissioner notes that there are very few clearly innocuous drug products or components in the OTC area. Several examples can be given: If appropriate stability study requirements and manufacturing controls required by CGMP regulations are not met for fluoride toothpaste, there could be a question of effectiveness of the products because of the unavailability of fluoride in a toothpaste.

In the case of aerosolized products, control of the particle size and identity and purity of components are important for the safety of the user. In the case of topical cosmetic-type drugs, the incidence of allergic reactions may be lessened by the assurance of uniform quality of these products. That many of the general CGMP regulations are applicable to and reasonable

for cosmetic-type drug products is evidenced by the fact that a majority of the specific suggestions submitted by the petitioner and others as applicable for cosmetic-type drug products duplicated in substance, a number of comments submitted by other OTC manufacturers and manufacturers of prescription drug products and the proposed text of part 211.

Although he declines to provide a broad exemption for cosmetic-type drugs products, the Commissioner points out that a number of changes proposed by the comments are adopted in the final regulations. These suggested changes were appropriate for application to the manufacture of all drugs products, however, and not merely cosmetic-type drug products. In many instances the suggested changes that were adopted do not alter the original intent of the regulations, but clarify it or provide flexibility in complying. In a few cases, the proposed requirements were deleted or changed where the Commissioner concluded that they were not necessary to assure the quality of drug products, cosmetic-type or otherwise. i. Drug products that are also foods.

Although no specific requests were received to exempt OTC drug products that are also human foods from Part 211, the Commissioner has tentatively concluded that there may be a few such products that would more appropriately be regulated under the good manufacturing practice regulations for food. He believes that the type of OTC drug products that could be exempted from Part 211 are those that are ordinarily marketed and consumed as human foods which may also fall within the legal definition of drugs by virtue of their intended use.

Therefore, elsewhere in this issue of the FEDERAL REGISTER, the Commissioner is proposing to exempt such products if the products and all their ingredients are ordinarily consumed as human foods. Examples of products that the Commissioner foresees being covered by the proposed exemption are (1) Some candy cough drops formulated entirely of ingredients ordinarily consumed as human foods or ingredients of human

foods; and (2) sodium bicarbonate labeled for use as an antacid but ordinarily use as an ingredient of human foods under the more common "baking soda" label.

In proposing this exemption for certain OTC drug products, the Commissioner has considered, first, the inadvisability of applying drug CGMP regulations that are not necessary to ensure appropriate quality characteristics in view of the intended use of a product and, second, the reasonableness of applying food GMP regulations to a product manufactured, handled, and ordinarily consumed as a human food.

Therefore, the Commissioner has stated under 211.1(c) that, pending considered of the proposal, the requirements of Part 211 will not be enforced for OTC drugs that meet the proposed definition. During the interim and until further notice, regulations under Part 110 (21 CFR Part 110) and, where applicable, Parts 113 to 129 (21 CFR Parts 113 to 129) shall be applied in determining whether these products are manufactured, processed, packed, or held under current good manufacturing practice.

43. One comment from a university school of pharmacy asked whether future proposed CGMP regulations would specifically state their applicability to such situations as (1) personnel at hospital "A" strip-packaging drug products for its own use as well as for use in hospitals "B" and "C"; (2) personnel at the warehouse of a chain of pharmacies who repackage and relabel quantities of drug products from manufacturers' original commercial containers for different units in the drug store chain; and (3) similar repackaging and relabeling by individual pharmacists as members of informal buying groups.

As noted in paragraph 42(g) above, section 501(a)(2)(B) of the act applies to retail establishments, pharmacies, and hospitals, but the specific regulations in Part 211 do not. When CGMP regulations for repackers and relabelers are proposed,

some of these questions posed in the comment will be addressed. Regarding pharmacies and hospitals in particular, however, it is the policy of FDA not to inspect routinely for compliance with section 501(a)(2)(B) of the act establishments that operate within State or local laws governing the practice of pharmacy.

Nor has FDA ever sought to issue specific CGMP regulations for pharmacies engaged in traditional activities of dispensing or selling drugs at retail. This policy is consistent with statutory exemptions provided for pharmacies regarding establishment registration in section 510(g) of the act and regarding establishment inspection in section 704(a) of the act. When a hospital or pharmacy is engaged in drug repackaging or relabeling operations that are beyond the usual conduct of dispensing or selling drugs at retail, however, the exemptions in the act cease to apply; the establishment is required to register and is subject to regular inspections under section 704 of the act.

Furthermore, appropriate current good manufacturing practice must be complied with. 44. Several comments expressed concern about the applicability of CGMP regulations to foreign drug manufacturers. One comment said foreign drug manufacturers may not uniformly be subject to the stringent controls of United States manufacturers and that sampling of foreign drug products at the point of importation is not sufficient to assure the quality of those drugs.

Two foreign drug manufacturers indicated that CGMP regulations had a significant impact on their operations. Another foreign manufacturer said their facilities were inspected annually by FDA with respect to antibiotic certification and new drug approvals. The act applies to drugs introduced into interstate commerce in the United States, including drugs imported from other countries. It does not, of course, apply to manufacturing of drugs in other nations if the drugs are not brought into the United States. Many foreign

countries, however, have adopted requirements similar to CGMP regulations, and foreign manufacturers may be subjected to inspection by their own governments.

International organizations such as the World Health Organization and the European Free Trade Association provide manufacturing standards and reciprocal agreements between participating countries. Overseas pharmaceutical manufacturers who export to the United States are inspected by FDA or under reciprocal inspection agreements as part of the new drug application approval process and antibiotic drug certification, and individual drug products are subject to intensive examination, including testing, before being allowed into the United States.

If, for example, there is a question regarding the safety, identity, strength, quality, or purity of a drug product offered for import, FDA has authority to deny entry of the article unless factory inspection is permitted or inspectional information is available about those firms covered under reciprocal inspection agreements.

The United State currently has reciprocal inspection agreements under which governments will exchange inspection information about domestic firms in lieu of conducting overseas inspections. These agreements are with Sweden, Switzerland, and Canada. Therefore, the Commissioner finds that there is adequate coverage of imported drugs to assure compliance with CGMP regulations.

45. Several comments referred to provisions in the Medical Device Amendments of 1976 and requested that FDA consider providing for exemptions from or variances to the CGMP regulations and special advisory assistance as Congress specifically mandated regarding FDA regulation of small manufacturers of medical devices. Along the same lines, a substantial number of comments were received from "small" drug manufacturers or organizations representing "small" drug

manufacturers who strenuously oppose most of the proposed changes in the CGMP regulations.

The tenor of the majority of the comments was that the proposed changes would seriously affect the initial and continuing costs of a "small" drug manufacturer but probably have little economic impact on, or could more easily be absorbed by, a "large" pharmaceutical manufacturer. Several comments expressed concern that generic drug manufacturers might be eliminated because they could not meet all the requirements of the proposed CGMP regulations and still compete in the marketplace.

Arguments were presented that, because small manufacturers very often are involved with the manufacture of a small number of products (frequently less potent over-the-counter preparations) and almost by definition have small physical facilities, limited equipment, and few personnel, extensive formal quality control procedures are unnecessary to assure high quality of the drugs manufactured.

One comment, apparently from a small manufacturer, agreed in principal with the proposed CGMP regulations, felt that size had very little to do with achieving good manufacturing practice, and offered comments on specific sections of the proposed CGMP regulations. The Commissioner rejects the contention that quality control procedures are unnecessary in the case of small firms; FDA's experience is that quality control procedures falling below those described in these regulations, in firms of great or small size, are often responsible for lack of drug product quality.

The Commissioner also rejects the argument that less control need be exerted over so-called "less potent over-the-counter preparations," which respondents stated are often manufactured by small firms, for the reasons explained in paragraph 42(h) above. The Commissioner believes that the

final regulations will be no more burdensome for small manufacturers than for others.

Many interpretations offered in comments on specific sections strongly suggested that the intent of the proposed regulations had been misunderstood. The language has been clarified in the final regulations. In other instances the requirements were reworded to provide for more flexibility for the varieties of procedures and controls that may be utilized by various manufacturers. The Commissioner does not believe a specific provision within the CGMP regulations for variances to these regulations is necessary for small manufacturers. A mechanism already exists, however, in 21 CFR 10.30 for firms to petition for variances to or amendments in any regulation when the requirements are not reasonably attainable.

For many years FDA has conducted and participated in numerous seminars and workshops designed to assist drug firms in interpreting and carrying out the requirements of CGMP regulations. Additionally, the agency has made films and publications available that are also designed to assist drug firms in their efforts to comply. The agency is committed to continuing these voluntary compliance efforts especially designed to assist small businesses.

46. Several comments noted that the current good manufacturing practice regulations do not pertain to veterinary biological products. One respondent suggested that the section specifically state that these regulations apply only to human biological products. The Commissioner believes that the section as proposed clearly establishes applicability to pertinent biological drug regulations, but for consistency with references elsewhere in the CGMP regulations to human biological drug products, he is revising 210.2 to specifically include reference to biological drug products for human use.

47. Several comments requested clarification of the last sentence of 210.2 to show that conflicting or contradictory

regulations would be superseded by the one specifically applicable to the drug product. The Commissioner finds that the proposed wording clearly states his intent. Certainly, in the case of conflicting or contradictory regulations, it will be impossible to comply with all regulations and the regulation that is specifically applicable to the drug product in question would apply.

48. A comment suggested that if medicated premixes are meant to be excluded from Part 210, then Part 226 should be specifically excluded. The meaning of this comment, as it relates to 210.2 is not clear. The Commissioner advises that Part 210 applies to all the regulations in Parts 211 through 229.

49. One person proposed that the term "drug product" be replaced with the words "commercial dosage form" to exempt drugs undergoing development from the requirements of these regulations. The Commissioner finds that, as stated in 211.1, these CGMP regulations apply to the preparation of any drug product for administration to humans or animals, including those still in investigational stages.

It is appropriate that the process by which a drug product is manufactured in the development phase be well documented and controlled in order to assure the reproducibility of the product for further testing and for ultimate commercial production. The Commissioner is considering proposing additional CGMP regulations specifically designed to cover drugs in research stages.

VII. DEFINITIONS

The Commissioner received hundreds of comments regarding definitions. General comments are listed immediately below; comments regarding specific definitions follow in numerical order.

50. One respondent said this section is inconsistent because certain terms such as "drug" and "establishment" which are defined in the act are not defined here, while other terms which are defined elsewhere are also defined here. The Commissioner believes that the length of part 210 would be unnecessarily increased by including in this part the definitions of terms that are well known or already defined in the act. Other terms the meaning of which may not be as readily recognized, or may vary in other regulations because of context and needs, are defined in part 210 as a standard reference.

51. One comment suggested that all terms defined in part 210 be highlighted in the running text. The Commissioner is not convinced that highlighting defined words in the running text offers any advantages over the more usual manner of printing. For example, some persons might interpret highlighting as adding emphasis that is not intended to a particular word or phrase. This suggestion cannot be adopted.

52. One respondent suggested rules for selecting words to be defined, namely: (1) Words which will be used in a sense differing from that given in the currently accepted dictionaries and (2) words whose meaning will be limited by the regulation. The Commissioner believes the above criteria have been generally used for selecting terms to be defined. He does not wish, however, to limit strictly the criteria for determining the terms to be defined in this part.

53. Several comments asked that commonly used terms such as "drug product containers," "labeling," and

"production area" be defined. The Commissioner finds that either the terms have already been defined elsewhere (e.g., "labeling," which is defined in section 201(m) of the act) or they are generally well understood and need no further definition (e.g., "drug product container"). He concludes that no further definitions need to be added at this time.

54. One comment suggested that "cycle of manufacture" be defined in 210.3(b)(2) as "any period of time in which the batch is not adversely altered."

The Commissioner has considered this comment, but does not find that the suggested wording offers any advantage. The definition, as it appeared in the proposal, has been in the CGMP regulations for a number of years. The Commissioner is confident that this definition is well understood.

55. Several comments suggested modification of the term "batch" in 210.3(b)(2) by addition of the words "is intended to have" before "uniform character." Another modification suggested was a new phrase at the end of the sentence: "Which is accepted and offered for sale or distribution." In defining a "batch," the Commissioner has adopted the phrase "intended to have uniform character and quality." Using the phrase "intended to have" in the definition allows the use of the term "batch" without having to distinguish between acceptable and unacceptable batches. If a manufactured batch does not have uniform character and quality within specified limits, then the batch becomes an unacceptable or a rejected batch.

The Commissioner rejects the phrase "which is accepted and offered for sale or distribution." Those batches which are manufactured but never intended for sale or distribution may be designated as trial or experimental batches by the manufacturer.

56. Three comments on 210.3(b)(3) requested that the term "component" be changed to "ingredient," stating that the former term has been used in the drug industry for "packaging supplies." The Commissioner recognizes that the term "component" is broadly used in the English language and may have a variety of meanings. However, the definition of this term in the proposal has been in effect for a number of years and the Commissioner believes it is generally well understood. Because only three comments were received regarding this particular issue, the Commissioner concludes that the drug industry generally does not find the term misleading.

Therefore, the recommendation is not adopted.

57. A suggestion was made that the definition for the word "component" in 210.3(b)(3) should include gases and filters, because these items need additional control when used in the manufacture of injectable products. The Commissioner notes that "component" includes gases that are used as ingredients. He believes filters are more appropriately classified as equipment.

The Commissioner believes that control of gases and filters is adequately set out in the regulations.

58. One comment suggested that the definition for "component" be expanded to include the phrase "raw material, chemical compound, drug substance or pharmaceutical ingredient." The Commissioner agrees that the above items when used as ingredients are properly classed as components. It is not necessary or desirable, however, to list each type of material that may become a component under the regulations, because items other than those identified in the comment may also be "components."

Therefore, the suggestion is not accepted.

59. A suggestion was received to include the following phrase after the word "manufacture" in the second sentence of 210.3(b)(3): "of finished dosage form, e.g. tablets, capsules, solutions, etc." The Commissioner rejects this suggestion. The term "drug product" is defined in paragraph (b)(4) of 210.3 as "a finished dosage form" and restatement of the definition is inappropriate.

60. Several comments requested clarification of the relationship among the definitions in 210.3(b) (3), (7), and (8) of "component," "active ingredient," and "inactive ingredient." Comments expressed concern that proposed definitions of the types of ingredients do not include all materials contemplated under the definition of "component." The Commissioner finds that the definition for "inactive ingredient" in 210.3(b)(8) should be modified so that it clearly includes "any component other than an active ingredient." He believes this change will eliminate any misunderstanding of these definitions.

61. One comment suggested that the term "drug product," as proposed in 210.3(b)(4), could be interpreted to mean only the finished packaged unit. The Commissioner finds that the term is defined as meaning "finished dosage form" regardless of whether it is in package form.

62. A comment was received stating that the term "drug product" as defined in 210.3(b)(4) excludes placebos because the definition includes the phrase "active drug ingredient." The intended use of placebos in medical treatment is to bring about a therapeutic effect, without a pharmacologically active agent, because of the psychic effect in some patients that may produce symptomatic relief.

In addition, it is often used as a control in clinical trials for new drugs. Even though the chemicals from which the placebos are made are not intended to cause a direct pharmacologic response, the maintenance of their quality is important because of their use in patients, particularly in controlled drug

studies. By its use, a placebo meets the definition of a "drug" contained in section 201(g) of the act. Therefore, to eliminate any doubt whether these regulations apply to placebos, the Commissioner has revised the definition to include them specifically.

63. A number of comments questioned the definition of "fiber" in proposed 210.3(b)(5). The comments were that "fiber" had been defined arbitrarily and without scientific basis; that the definition was too general and could include, for example, crystal, metal and splintered wood; and that the definition should include dimensional parameters for the fiber size. Comments recommended that the definition include morphological descriptions such as threadlike, filamentous, amorphous or noncrystalline, cellular, foreign, and hairlike.

Several comments recommended that the American Society for Testing and Materials definition be used. Others suggested that a length of at least 100 microns and a length/width ratio of 10 to 1 be adopted. One comment called for adopting a minimum length of 10 microns and a diameter one-tenth the length. The Commissioner finds that the term "fiber" has not been defined arbitrarily and without scientific basis.

The basis for the fiber definition was discussed in the final regulations for asbestos-form particles in drugs for parenteral injection, which appeared in the FEDERAL REGISTER of March 14, 1975 (40 FR 11865). (Those final regulations reference the definition of "fiber" appearing in "Occupational Exposure to Asbestos," criteria document, U.S. Public Health Service, National Institute for Occupational Safety and Health, Chapter VIII, p. 6, 1972). The Commissioner believes that the definition should be as broad as possible and that the suggested morphological descriptions and dimensional parameters are unnecessary and in many instances are not informative.

Dimensional parameters were intentionally left out because current knowledge is limited as to what size fiber does not constitute a hazard. Furthermore, the suggested fiber length of at least 100 microns is unacceptable because most asbestos fibers released from asbestos-cellulose filters are less than 70 microns in length. The American Society for Testing and Materials' specifications (ASTM Manual F24-65, Standard Methods for Measuring and Counting Particulate Contamination on Surfaces) for defining "fiber" are not pertinent to the subject at hand.

They were developed specifically for particles on surfaces of mechanical objects as related to abrasion of such objects. To eliminate any concern that the definition of fiber would include particles intentionally present, as in drug suspensions, the final regulation is modified by adopting the concept of particle contamination. Therefore, fiber means any particulate contaminate having a length at least three times its width.

64. Comment was received regarding 210.3(b)(6) that the definition for "non-fiber-releasing filter" should include the concept of a filter "being designed" not to release fibers after appropriate pretreatment. Another comment said a requirement for non-release of fibers is unrealistically absolute, i.e., no known filter could meet the definition. The Commissioner advises that the final regulation adopting the definition for "non-fiber-releasing filter," published in the FEDERAL REGISTER of March 14, 1975 (40 FR 11865), addressed similar issues. In responding to comments in that document, the Commissioner concluded the definition should include the concept that after appropriate pretreatment such as washing or flushing, the filter will not continue to release fibers into the drug that is being filtered. The design concept is therefore taken into account because of the distinction made between filters which release fibers by media migration, i.e., continuous release due to the nature of the filter, and filters which contain fibers from structural supports and contamination. With regard to the comment that the

requirement for non-release of fibers is unrealistically absolute, the Commissioner finds that the definition clearly describes types of fibers that are relied upon in the industry as "non-fiber releasing." The Commissioner concedes that any filter may release an occasional particle, some of which may meet the definition of "fiber" under 210.3(b)(5). The purpose of the definition for "non-fiber releasing filter," which has been applied for over 2 years without apparent misunderstanding, is to provide a reasonable and practical description of a filter that may be fabricated from a number of different materials and will not, in the ordinary sense, introduce fibers into the drug product during filtration.

As discussed in detail in the preamble to the March 14, 1975 final regulation adopting the definitions for "fiber" and "non-fiber releasing filter", FDA is studying several issues involving fiber contamination and the effects on humans to fiber exposure. Until such time as the Commissioner has obtained sufficient information to alter his position on fiber contamination in parenteral drug products without adversely affecting the public health, he concludes that the definition for "non-fiber releasing filter" continues to be appropriate for these regulations.

65. Comment was received that the definition of "non-fiber-releasing filter" as written in 210.3(a)(6) would discourage the development of asbestos filters that might not be fiber releasing. The Commissioner advises that it is not the intention of FDA to discourage the development of asbestos filters. In this regard, the preamble to the final order in the FEDERAL REGISTER of March 14, 1975 (40 FR 11865) addresses this issue in detail. 66. One comment suggested that "non-fiber-releasing filter" be redefined to apply only to the final filtration of components and drug products.

The Commissioner concludes that the suggestion would allow use of an asbestos filter for filtration of in-process materials. This use of asbestos filters is unacceptable, except under the

provision of 211.72(b), and would defeat the purpose of the regulation.

67. A comment suggested that after the word "component" in 210.3(b)(7) the phrase "other than veterinary biological immunizing or diagnostic agent" should be added. The Commissioner finds that articles that are not deemed drug products or that are not under the jurisdiction of the act are not subject to these regulations. It is not desirable or feasible to identify in these regulations every specific class of articles that are not subject to CGMP regulations. Veterinary biologicals have, however, been excluded by changes in 210.2. When an interested person has a question regarding the status of another individual product or class of products (for example, the status of an article that may be either a drug or a device), that person may obtain a formal opinion from FDA pursuant to 21 CFR 10.85.

68. Several comments asked that limits be placed on the term "in-process materials" defined in 210.3(b)(9) in order to restrict it to those materials generated "in-plant" as opposed to those materials acquired from an outside source. The Commissioner agrees that the term "in-process materials" is intended to apply to materials being processed by establishments engaged in the preparation of a drug product. He believes this intent is clear when the term is considered in the scope of these regulations and that no change is needed.

69. Several comments requested clarification whether the term "in-process materials" in 210.3(b)(9) includes labels printed "in-house" and other "nonchemical" items. It was not the Commissioner's intent that "in-process materials" include label printing. The regulations do not suggest that such labeling would constitute in-process materials. References to labeling materials are clearly stated in these regulations when appropriate.

70. One comment suggested that the word "materials" in 210.3(b)(9) be changed to "ingredients." The Commissioner concludes that the term "in-process materials" is in current usage and sees no advantage to introducing the suggested term "in-process" ingredients."

70a. One comment stated that 210.3(b)(9), and especially the word "fabricated" is unclear and should be further defined to eliminate any possible confusion. The Commissioner does not agree that the word "fabricated" is unclear when used in this definition. This suggestion is rejected because a broad term such as "fabricated" is appropriate here.

71. Several comments said, in the case of biologics, a "lot" may consist of more than one batch and suggested that this be included in the definition of "lot" in 210.3(b)(10). Because the term "lot" has already been defined specifically for biological products in 21 CFR 600.3(x), the Commissioner does not believe that any modification of the definition in this part is appropriate. As previously indicated, the more specific regulations for biological drug products take precedent over the more general.

72. Two comments said the term "lot" was used elsewhere in the CGMP regulations (e.g., 211.84(a)) to refer to containers and closures, which are neither drugs nor drug products. They said either the definition in 210.3(b)(10) or the reference was incorrect. The Commissioner notes that the definition in 210.3(b)(10) refers to the term "drug product," but does not limit to drug products the applications of the definition for "lot."

However, the proposed definition for "batch" is limited to drugs. Because a lot is defined as a batch or portion of a batch, the definition for "batch" is expanded to include materials other than drugs. Similarly, the definition for "lot number" is expanded to include other materials.

73. One comment said the definition for "lot number" in 210.3(b)(11) unnecessarily ruled out the use of symbols. It was not the Commissioner's intent to preclude the use of symbols, and the definition is modified accordingly.

74. One comment suggested deletion of the word "complete" from 210.3(b)(11) as superfluous and subject to interpretation. The Commissioner finds that use of the phrase "complete history" emphasizes that pertinent identifying information is included.

75. Two comments suggested that the words "testing, and quality control of drug products" be deleted from the definition in 210.3(b)(12). One said these functions do not belong in this definition because they introduce ambiguities elsewhere in the proposed regulations.

Examples given are: (1) 211.103, which requires yield determination at the end of each distinct phase of manufacturing; and (2) 211.67(b), which requires that procedures describe a cleaning schedule for all equipment used in manufacturing, processing, packaging, or holding of a drug product.

The respondent said yield calculations and cleaning schedules do not apply to laboratory testing and equipment. Another respondent said the words "testing and quality control of drug products" should be deleted because they conflict with the concept of independent responsibility for quality control and manufacturing functions.

The Commissioner sees no ambiguities arising from the inclusion of "testing and quality control of drug products" in this paragraph. Indeed, comments were received on numerous sections of the regulations (e.g., 211.2 (recodified 211.68) and 211.25) to add the phrase after references to "manufacture, processing, packing and holding." In all cases, the Commissioner has declined to make the addition.

The purposes of this definition are to make it clear that the phrase "manufacture, processing, packing, or holding of a drug product" includes operations that are commonly known by other terms such as "packaging," "labeling," or "quality control," and to eliminate the need for inserting references to testing and quality control throughout the text of these regulations. Section 211.103 is modified to provide that yield determinations are not required for quality control activities.

The Commissioner believes, however, that the requirements of 211.67(b) are appropriate for quality control operations. The Commissioner believes that the functions of quality control and manufacturing can be included in the total concept of producing drug products and still be independent.

The comment did not describe how the definition would actually cause a loss of independence of the quality control function.

76. One comment suggested that the term "warehousing" was more suitable than the term "holding" in 210.3(b)(12). The Commissioner finds that, although the term "warehousing" describes the meaning intended some of the time, the more general term "holding" is more suitable. The Commissioner also notes that the entire phrase "manufacture, processing, packing, or holding" is repeated from section 501(a)(2)(B) of the act.

77. One comment said the term "quality control" is too vague in 210.3(b)(12) because it does not cover the responsibilities of other than the quality control department. The comment suggested the following wording:
"Manufacturing, processing, packaging or holding of a drug product includes packaging and labeling operations, testing and other measures taken to insure that the drug product has the identity, strength, quality and purity which it purports to or is represented to possess."

The Commissioner does not agree that the definition is vague. The intent is to identify several key operations that might not be perceived as an integral part of the production of pharmaceuticals, but for purposes of CGMP regulations must be included. It is not necessary, however, to describe every operation that is included under the act. The responsibilities of the quality control unit are specified in 211.22 and are not affected by this definition.

78. Several comments said the definition in 210.3(b)(15) of a "quality control unit," taken together with its responsibilities, would mean that the quality control unit would duplicate functions such as engineering, which are better handled by other professionals such as engineers. They also said the term "unit" generated confusion vis-a-vis the "quality control department" and "quality assurance department." Another comment said the word "perform" should be replaced with "be responsible for."

Functions that are properly those of the engineering department or other specialized units because of their unique training and expertise should not be duplicated or usurped by the quality control unit. Where expertise is in other units, the responsibility of the quality control unit is to assure that such expertise has been utilized. In order to make clear that quality control functions may be performed by persons assigned to units outside the quality control unit, the Commissioner is replacing "perform" with "be responsible for."

The quality control unit will still have the duty to assure that appropriate actions were implemented and completed satisfactorily. The Commissioner used the word "unit" 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.

79. Several comments suggested use of the term "expected yield" instead of "theoretical yield" in 210.3(b)(17) and in 211.192. They also suggested that the definition include a provision for normal and expected losses. The terminology and concept of "theoretical yield" appear to be understood and generally used in the pharmaceutical industry. The Commissioner notes that the regulations (e.g., 211.186(b)(7) and 211.192) allow for normal and expected losses before investigations or corrective actions are required. The concept of theoretical yield is important as a basis upon which actual or expected yields can be compared to the theoretical yield to aid determining acceptance.

80. One comment said the definition of "theoretical yield" is nonspecific in the wording "quantity of components to be used." A suggested alternative wording was "quantity of component specified by master production records for that operation." The Commissioner sees no need for the suggested revision in the definition section. The requirement for compounding in accordance with master production records is covered elsewhere in these regulations.

81. One comment suggested insertion of the word "distinct" before the word "stage" in paragraphs (b) (17), (18), and (19) of 210.3 because yields cannot always be determined at any stage of manufacture. Another comment said establishing theoretical yield is not always possible for certain processes involving chemical reactions and production of biologicals. The Commissioner believes that a theoretical yield can be established for all processes.

The theoretical yield for a chemical reaction, for example, would be maximum yield obtainable under optimal reaction conditions. The Commissioner agrees that the word "stage" may not adequately define the phase of manufacture at which the theoretical yield should be determined. Therefore, he is adopting the phrase "appropriate phase" in paragraphs (b) (17), (18), and (19) of 210.3.

82. A number of comments have been received regarding proposed paragraphs (b) (21), (22), (23), and (24) of 210.3.

As discussed elsewhere in this preamble, the Commissioner is not including in these regulations, at this time, specific requirements regarding "acceptable quality level and unacceptable quality level"; therefore, definitions for these two terms are deleted from the final regulation. Proposed paragraph (b) (21) and (24) is being retained, however, with modifications, as 210.3(b) (20) and (21).

83. One comment suggested including in the proposed definition of "acceptance criteria" (proposed 210.3(b)(21)) the sentence: "Such acceptance criteria may be altered if evidence demonstrates that a valid reason exists for establishing revised acceptance criteria following an appropriate documented quality assurance conference." The Commissioner notes that the proposed definition, now 210.3(b)(20), would not preclude a change in product specifications or acceptance criteria if such change is appropriate. There is no need to incorporate the proposed language.

84. One comment suggested elimination of the word "reject" from proposed 210.3(b)(21), stating that material which is not accepted may be reworked or returned to the supplier. The Commissioner does not agree with this suggestion. The term "reject" does not denote the ultimate disposition of the product, only that it is not acceptable for use as is.

85. One comment suggested that "sampling plans," referred to in proposed 210.3(b)(21), are not the only technique used to form a basis for acceptance and rejection. The Commissioner has used the term "sampling plan" in a

broad context here. The term can mean both a plan for collection of physical units for testing, or it can mean a schedule by which an examination of some sort is done.

86. Numerous comments said the term "at random" should be deleted from proposed 210.3(b)(24). Among the reasons given were that "random" has a limited meaning in statistics, that some samples are best taken on a stratified basis, such as right after each start-up of a run, and that some samples are taken on a timed basis. The Commissioner is persuaded that the term "at random" without additional clarification may be too limiting for this definition and modifies the final regulation accordingly.

87. In reviewing the proposed regulations, the Commissioner concludes that 211.2 and 211.68 should be combined into a new 211.68. Proposed 211.2 is deleted, and the substance of the requirements is included in the new 211.68. The comments relating to 211.2 are discussed with those for 211.68. **88.** Three comments were received regarding proposed 211.3 on definitions for Part 211. Two comments said the section is duplicative and should be deleted.

The other comment noted that some of the words defined in referenced 210.3 are not used in Part 211. The Commissioner finds that the reference to 210.3 that appears in 211.3 is valuable as a cross reference. In addition, he anticipates a need for a definition section in each part of the CGMP regulations to accommodate terms specific to that individual part but not others.

This scheme has already been used in the proposed CGMP regulations for Part 212 relating to large volume parenteral (LVP) drug products, published in the FEDERAL REGISTER of June 1, 1976 (41 FR 22202). The Commissioner sees no inconsistency in that terms defined in 210.3 may not be used in Part 211, because they may be used in other parts (e.g.,

Parts 225 and 226). The definitions apply only where the term is used.

VIII. ORGANIZATION AND PERSONNEL

89. One comment argued that as written, the regulations (211.22-211.34) permit the subordination of the quality control unit's function to any other unit designated by management, including the production unit. Such a subordination of quality control to production was described as a conflict of interest. The Commissioner does not agree. The CGMP regulations do not subordinate the quality control unit's authority and responsibility to any other unit.

At the same time, the regulations regarding the quality control unit does not encroach upon the expertise or responsibility of other units in a firm and do not dictate the organizational structure of a firm. They simply require that the quality control unit have final responsibility for certain actions in the manufacturing process.

90. One comment suggested that CGMP regulations assign individual certification responsibility to persons within the organization. This would include responsibility for review of product specifications and control procedures to assure their adequacy and reliability. The Commissioner notes that such control responsibilities are already assigned in these regulations to the quality control unit. "Certification" is not specifically required as something more than approval by the quality control unit. Assignment of individual responsibilities within a firm should be left to the discretion of management.

RESPONSIBILITIES OF QUALITY CONTROL UNIT

91. Comments contended that 211.22, as proposed, would unreasonably interfere with management's right to structure its organization as it deems fit. In addition, it was pointed out that quality control responsibilities are often performed by units of the firm other than the quality control unit; examples cited were formulation designed, development of the manufacturing process, and process control design by

research and development scientists, engineers, and other manufacturing specialists.

The duties outlined in the proposal for the quality control unit were described as duplicative of functions performed with more expertise in other segments of a firm. The Commissioner intends to make the quality control unit responsible for ensuring that controls are implemented during manufacturing operations which assure drug product quality, not that the quality control unit actually perform each one of the duties. The Commissioner believes that, even under 211.22, management has the prerogative to organize its internal structure and assign responsibilities as it deems appropriate, as long as some identifiable person or unit has at least those responsibilities assigned by the regulations to the quality control unit. To clarify that the quality control unit could not and should not perform duties duplicative of other parts of the organization, the Commissioner has modified the definition of "quality control unit" in 210.3(b)(15).

The word "perform" has been deleted and the phrase "be responsible for" substituted. Additional clarification of the Commissioner's position regarding these comments may be found in the preamble discussion under paragraph 78 of this preamble.

92. One comment asked that the responsibilities of the manufacturing units be defined. As long as provision is made in these regulations for the assignment of certain quality control activities to a quality control unit, the Commissioner believes that other assignments should be at the discretion of individual firm's management.

93. A comment made a distinction between a quality control department and a quality control unit and questioned what duties would be assigned to each. Several other comments suggested that this section dealing with quality control units was primarily designed for large pharmaceutical

firms and did not take into consideration that small firms could not comply.

The distinction made between "department" and "unit" is not required by the regulation, which does not specify a name for the quality control unit, but merely describes several responsibilities that a designated unit must have. The organizational structure of the unit is left up to each individual firm's needs. A small firm may choose a different means of structuring its organization. The term "quality control unit" is defined in 210.3(b)(15) as any person or organizational element. This means that in very small operations a single individual can function as the quality control unit. But that person still has the responsibility for implementing all the controls and reviewing the results of manufacturing to assure that drug product quality standards have been met.

As discussed above in paragraph 45, the Commissioner rejects the idea that quality control is not needed in a small business.

94. A comment was made that this section precludes the use of outside consulting laboratories for quality control work. The Commissioner disagrees. There is no such prohibition in the regulations. A manufacturer does have a responsibility, however, to see that the outside laboratory used is qualified to do the work and that the work is performed satisfactorily.

95. With respect to the quality control unit's authority and responsibility under 211.22(a) for approval and/or rejection of raw materials, in-process materials, and finished products, one person asked that other alternatives be permitted when materials may be suitable for other purposes and uses than those originally intended. Use of the word "reject" does not necessarily mean that the rejected material must be destroyed.

When materials are ordered by a manufacturer, they are ordered with a particular purpose in mind. If testing of a material shows that it is not suitable for a particular use, it may be used for that purpose and, therefore, is rejected. It may, however, be suitable for other uses requiring a material with differing specifications.

96. Several comments proposed that 211.22(a) be modified so that the quality control unit would not have to have the responsibility to review all labeling unless it is connected with the manufactured dosage form. The reasoning was that some promotional literature, not physically associated with the drug product, had been defined as labeling in court suits where FDA charged misbranding of a product with promotional literature, but that such material was not labeling in the sense in which these regulations referred to labeling.

The Commissioner notes that the scope of the CGMP regulations is to set forth the facilities, methods, and controls to be used for the manufacture, processing, packing, or holding of a drug product. It is not the purpose of the CGMP regulations to control labeling such as promotional literature that is not associated with the drug product during its preparation under CGMP regulations.

97. Comments asked for modification in the last sentence of 211.22(a) relating to production of drugs under contract by another company. They suggested that the contractor could release drugs for distribution on his own responsibility if a certificate of analysis showed compliance with appropriate specifications. Others suggested that the responsibility for approving or rejecting drug products produced by contractors appeared in this paragraph to rest with the contractor.

This paragraph clearly says that the quality control unit of a contracting firm must approve or reject drug products produced by contractors. The Commissioner believes this is

proper because, in the circumstances described, the contractor does not own the goods, but merely performs a service for the contracting firm. The responsibility to approve release of a drug product for distribution must rest with the owner of the drug product.

98. A number of persons responding to the proposal objected to the example of bioequivalence testing as one of the tests which must be performed in a quality control unit's laboratory. Some said this type of testing was normally done outside the quality control unit, such as by a medical unit. Others complained that bioequivalence standards are in a state of flux and have not as yet been established.

Bioequivalence tests may include tests such as dissolution tests, which are generally done in the quality control unit's laboratory. They also may include in vivo tests done by medical units within or outside the firm. The Commissioner agrees, therefore, that this example is not necessarily one which generally represents the work done in the quality control laboratory. Although he is deleting the bioequivalence testing example, in vitro dissolution tests for bioequivalence are in fact an example of the type of work that could and should be done in the quality control laboratory.

99. Two comments suggested either deleting the reference in 211.22(b) to "packaging materials" as one of the articles tested in the quality control laboratory, or changing it to "packing materials," on the basis that the examination for suitability of such materials is more properly a function of the shipping department and relates solely to protective qualities to prevent mutilation or breakage of drug product containers. Breakage of containers can cause product adulteration and mutilation of containers, which may result in product misbranding.

The protection of drug products from such mechanical damage is just as much a function of the maintenance of drug product

quality as placing light-sensitive products in light-resistant containers or labeling a product with its proper name and an accurate statement of its potency. The Commissioner notes that primary responsibility for selecting specifications for packaging materials may be assigned to the shipping department of a firm.

Under 211.22, the quality control unit is only responsible for testing and approving (or rejecting) packaging materials in accordance with these specifications. Therefore, no change is needed in the section.

100. Several comments proposed eliminating from 211.22(b) the statement regarding approval (or rejection) of materials used in manufacturing and suggested use of words like "evaluation" or "disposition." It was also suggested by others that "or" be placed between "and" and "approval" to allow for instances described as not requiring testing for approval. Several discussions appear in this preamble relating to the use of the words "approval" and "rejection."

These words mean either that an article may or may not be used for production of a drug product. Reprocessing, reworking, refining, diversion to other acceptable uses, returning to the supplier, or destruction are all actions that may occur after a decision to reject and are in no way precluded by the rejection decision unless specifically stated by the manufacturer.

101. Clarification of the option of using an outside testing laboratory was asked by respondents who wanted an explicit statement in 211.22(b) of the acceptability of this means of product examination. The thrust of 211.22(b) is that adequate laboratory facilities shall be available to the quality control unit from whatever source. The paragraph does not require those facilities to be owned and operated by the drug product manufacturer, nor does it prohibit the manufacturer from using a contract testing facility.

The Commissioner does not feel clarification is needed in 211.22(b).

102. Four comments recommended deletion of 211.22(c) entirely, because either (1) the requirements are adequately covered in 211.22(a), or (2) units of a firm other than the quality control unit have greater expertise in specific areas. The provisions of paragraph 211.22(a) differ from those of paragraph (c) in that paragraph (a) relates to the actual production of a product, while paragraph (c) covers events which occur before production.

The Commissioner realizes that not all expertise rests with the quality control unit, and he does not believe that the quality control unit should be solely responsible for developing and implementing all procedures and specifications impacting on drug product quality. A manufacturer may assign primary and initial responsibility for selecting procedures or specifications to the persons or units it believes most qualified. The Commissioner's intent is that the quality control unit be responsible for making sure that the procedures and specifications developed are appropriate and followed.

103. One comment indicated that the proposed 211.22(c) does not allow minor equipment changes that do not bear on drug quality, unless such changes are first approved by the quality control unit. Section 211.22(c) is limited to those procedures and specifications that impact on drug quality.

Moreover, the paragraph does not prevent the production personnel from making minor equipment adjustments that may affect drug quality without the quality control unit's approval of the specific change. It does require that the procedures regarding such equipment adjustment be reviewed in advance by the quality control unit.

104. A comment suggested that 211.22(c) be expanded to provide for specification committees, formula committees, and others instead of making the quality control unit totally responsible. As already explained, input into specifications and procedures may come from any appropriate source. If a firm chooses to utilize specification and/or formula committees, it is not prohibited from doing so by these regulations.

105. One firm suggested rewording of 211.22(d) to eliminate the word "responsibilities" and to add the word "routine" before "procedures." It was suggested that the paragraph as proposed is too broad and that responsibilities for the quality control unit are described elsewhere. Section 211.22(d) does not define the responsibilities of the quality control unit, but it does require that all its responsibilities, including those required in 211.22, be in writing. For consistency with other sections in the CGMP regulations, the phrase "such written procedures shall be followed" is being added to 211.22(d).

PERSONNEL QUALIFICATIONS

106. One comment said 211.25 is replete with vague terminology, which sets the stage for arbitrary and capricious actions by FDA, thereby placing individuals and companies in a position of unnecessary risk. Two comments stated that this section is one in which FDA attempts to replace management's judgment with regulations.

The Commissioner believes that this section must be of a general and flexible nature to allow management to exercise its prerogatives in light of the various types and sizes of firms, the products made, the differing personnel qualifications needed, the training programs which may be instituted, and other factors.

Although such generality will require more judgment to be exercised by FDA investigators who make plant inspections, it

does not permit any arbitrary or capricious action by the agency. In addition to the fact that all sanctions authorized by the act may only be enforced through judicial process, FDA is further defining its policy and standards for regulatory action in a series of regulations set forth in 21 CFR Part 7. The Commissioner believes this is ample protection against unreasonable actions by agency personnel.

107. Many comments questioned the frequency of the "continuing training" required in 211.25(a), asked for a definition of the word "continuing," and questioned who should receive what type of training. The requirement that training be on a continuing basis is intended to mean, for example, that a single training course at the time an employee is hired, with no subsequent training activities, is not sufficient. Subsequent training should be sufficiently frequent to assure that employees remain familiar with CGMP requirements. The Commissioner does not believe it would be prudent to specify time intervals for training in view of the broad nature of the drug industry and the wide range of employee functions covered by these regulations. The Commissioner believes this section is sufficiently clear in identifying "who should receive what training" in stating that each person engaged in the manufacture, processing, packing or holding of a drug product must have training in current good manufacturing practice that relates to that person's functions in the firm.

The requirements of 211.25(a) apply to supervisors as well as other employees; 211.25(b) contains an additional requirement for supervisory personnel.

108. Numerous comments pointed out that paragraphs (a) and (b) of 211.25 are not consistent in that 211.25(b), but not paragraph (a), contains the phrase "or any combination thereof" following the phrase "education, training, and experience." Most argued that 211.25(a) should also contain this phrase.

The intent of the requirement is that a person have a sufficient mix of training, education, and experience to perform his or her job adequately. What is adequate in regard to each of the criteria depends on the job. It may be that a person can adequately perform a particular job with very little or no previous experience, or limited education, or with minimal training, depending on the demands of the job and the qualifications of the person. Because the intent of this section has been misinterpreted, 211.25(a) is revised to include the phrase "or any combination thereof" and be consistent with paragraph (b).

109. One comment questioned how much education, training, experience, or combination thereof qualifies a person to be a supervisor under 211.25(b). The Commissioner believes it should be understood that broad regulations such as these could not reasonably quantify the degree of education, training, and experience necessary. It is left to management's reasonable judgment as to what constitutes sufficient background in these criteria so that supervisors can perform their assigned functions in a manner to provide assurance for the quality of drug products within their purview.

110. One comment on 211.25 (a) and (b) said it would mean little for some individuals to be instructed in the legal and technical language of the regulations. The respondent indicated that it is more important that personnel be instructed in the principles of good manufacturing practice relevant to their particular tasks. Section 211.25 requires training in current good manufacturing practice as it relates to an employee's function.

The Commissioner intends that training be meaningful to the employee, not a formalistic but useless exercise to satisfy a regulation. The requirement is written to provide reasonable latitude to a firm as to the extent to which technical and legal instruction will be given.

111. A number of comments said the requirement in 211.25(c) for "an adequate number of personnel" does not belong in the section on personnel qualifications. The Commissioner notes that the intent of this paragraph in relation to the number of employees is that there be an adequate number of qualified personnel. The Commissioner is revising this paragraph in the final regulation by inserting the word "qualified."

PERSONNEL RESPONSIBILITIES

112. One comment said all persons who enter the manufacturing, processing, packing, and holding areas should comply with the requirements of 211.28 and the section should reflect this. The Commissioner agrees that all persons, whether employees or not, who engage in the activities covered by this section should comply with the requirements of the section. Therefore, the Commissioner is replacing the word "employees" with the word "personnel" in 211.28 (b) and (d).

The Commissioner recognizes that not all persons who enter manufacturing areas are engaged in activities covered by CGMP regulations (e.g., equipment manufacturer service representatives and FDA investigators), and their activities would not be limited by 211.28. Drug manufacturers are responsible, however, for monitoring such activities to prevent contamination of drug products.

For example, all personnel entering a sterile area would be required to wear appropriate protective apparel.

113. One comment said 211.28 is an additional example of the agency's attempt to legislate and enforce regulations which must be left to the discretion of corporate management in order to preserve our free enterprise system. The Commissioner does not perceive how these regulations present a threat to the free enterprise system. These regulations were promulgated under the authority of section 501(a)(2)(B) of the

act, which was passed by the Congress in 1962 in order to assure that no drug product available to consumers was adulterated.

The requirements of the regulations are a reasonable and necessary step toward that goal. They do not inhibit competition, but rather enhance it by assuring that no manufacturer can reduce costs by eliminating those steps integral to the prevention of adulterated products. Thus, the consumer is assured that all marketed drugs meet the essential standards of identity, strength, quality, and purity; and consequently, selection of drugs by the consumer (directly or with the advice of a physician or pharmacist) will be based on fair principles of competition and free enterprise.

114. One comment suggested that in order to make it clear that facial hair coverings should be worn only if necessary, the second sentence of 211.28(a) should be reworded to read as follows: "They shall wear appropriate head coverings, including facial hair coverings, as necessary to prevent contamination of drug products."

The Commissioner recognizes that clarification of 211.28(a) is desirable and is therefore revising it to require that protective apparel, such as head, face, hand, and arm coverings, shall be worn as necessary to protect drug products from contamination.

115. One comment argued that the meaning of 211.28(a) is directed to human drug products and should be clarified to limit its scope accordingly. The Commissioner rejects this comment. These regulations are broad and consider the fact that certain drug products, regardless of whether they are for human or veterinary use, require the same amount of care in manufacturing, processing, packing, or holding in order to assure their safety and effectiveness.

The wording of this section requires precautions to be taken as necessary to protect the particular drug products from adulteration or contamination. The degree or types of precautions will depend on the particular drug product being considered.

116. One comment suggested rewording 211.28(a) by inserting the underlined statement: "Arms and hands shall be covered or other appropriate measures taken when microbial contamination is a concern when necessary to protect the drug product being handled"; and that this "appropriate measure" could mean the cleaning of the arms and hands with an antiseptic soap or solution as an alternative. The Commissioner rejects this alternative wording since it would alter the intent of this paragraph.

The possibility of microbial contamination is not the only reason for wearing protective apparel; prevention of particulate contamination, for example, may be of equal importance. Further, the Commissioner does not believe the phrase "as appropriate" would clarify this section since, as written in the final regulation, it clearly states that protective apparel shall be worn as necessary to prevent contamination of the drug product.

This paragraph does not preclude other measures such as cleaning which might be used in place of or in conjunction with protective apparel. If alternate methods were at least as effective as protective apparel, then protective apparel would not be necessary.

117. One firm commented on 211.28(a) that because of its type of operation it does not require, nor does it think it is necessary to have, uniforms if clothing is kept clean. The Commissioner notes that this paragraph does not necessarily require the wearing of uniforms. The requirement is that clothing be clean enough to be appropriate for the type of duty or operation being performed. For certain types of operations,

uniforms may be appropriate, while for other types of operations uniforms may not be necessary.

118. Several comments noted that 211.28(a) states in part that "they shall wear appropriate head coverings as necessary, including facial head coverings as necessary ***." And the comments argued that this statement is "too broad as written since facial hair includes eyelashes, eyebrows, etc." The Commissioner intended that this paragraph be broad enough to require the covering of eyebrows and eyelashes if necessary to prevent drug product contamination. Although he recognizes that this type of protection would not be usual for most operations, he would not wish to preclude the use of such measures.

119. Several comments argued that, with regard to arm coverings, there are certain kinds of machinery and equipment which present a personal hazard to workers using arm and hand coverings. The Commissioner recognizes that the use of arm and hand coverings could constitute a significant hazard if used around certain types of machinery. Appropriate alternatives can be used in such instances so that neither personnel safety nor drug product quality is compromised.

120. A comment noted that the term "authorized" in reference to personnel who may enter limited access areas is not defined in 211.28(c). The Commissioner believes that drug firms can reasonably determine on an individual basis which personnel should be permitted to enter what areas. The intent of this paragraph is to prevent the type of situation, for example, where persons not trained in aseptic techniques enter aseptic processing areas for reasons not associated with aseptic processing of the drug product.

To clarify that the authorization derives from the manufacturer, not FDA, the language of 211.28(c) is modified slightly.

121. One comment suggested that the word "may" in 211.28(d) be replaced by the words "is likely to" in order to identify realistically the threat of illness or lesions. The Commissioner rejects this alternative wording because the phrase "is likely to" is not strong enough to state the intent of this paragraph. Further, the alternative phrase would introduce the element of prediagnosis by the employee's supervisor.

While supervisory personnel can reasonably be expected to recognize health conditions that may affect the drug product, they probably would not be able to recognize conditions that are likely to affect the drug product. This may require more sophisticated evaluation by medical personnel. Of course, if medical personnel determine that the employee's health condition will not affect the drug product, the employee may resume his or her routine activities.

122. One comment argued that the words "they consider" be deleted from the last sentence of 211.28(d) because the reporting of conditions should not be limited to conditions which an employee thinks may affect the product. Another comment said the word "health" should be inserted between the words "any" and "conditions" in this sentence.

The Commissioner agrees that the intent of this paragraph is better served without the phrase "they consider" and with the addition of the word "health" and has revised the final regulation accordingly.

123. Several comments said 211.28(d) should not be construed to imply that supervisors are medically qualified to judge health conditions of employees. The Commissioner does not believe the paragraph implies this. Within the framework of industrial management, the supervisor is the liaison between the operating employee and higher echelons of the company.

It is the supervisor who is most likely, on a day-to-day basis, to notice health conditions that may affect the drug product. Of

course any such conditions noted initially by the supervisor may require evaluation by qualified medical personnel. Such medical evaluation is acknowledged in the final regulation. This section could perhaps set out more detailed procedures for dealing with employee health problems. But in the absence of significant difficulties in the area, the methods for dealing with health problems, beyond the initial phase of removing suspect employees from direct contact with drug products and their components, are left to the reasonable judgment of individual firms.

CONSULTANTS

124. Several comments were received requesting deletion of 211.34 because the ultimate liability for actions taken based on the advice of consultants still rests with the responsible officials of the drug product manufacturer. The argument is that a firm's choice of consultants should be a matter of its own judgment and not one of Government review or regulation.

The comments also state that FDA lacks authority under the act to prescribe qualifications for consultants. The Commissioner considers that consultants, while they are retained by the firm, are persons engaged in the manufacture, processing, packing, or holding of a drug product, and may lawfully be subjected to appropriate standards of qualification to the same extent as full-time employees of the firm.

Therefore, consultants must have education, training, and experience, or any combination thereof, sufficient to perform their assigned functions. Minor editorial amendments have been adopted in the final regulation to clarify this requirement.

125. Several comments requested that 211.34 state that the requirements are applicable only to consultants who are retained for activities that relate to the scope of the CGMP regulations. The Commissioner acknowledges that activities

that are not under the scope of the CGMP regulations should not be subject to such requirements. The final regulations are clear in this regard.

126. One comment asked that the term "consultant" be better defined in 211.34 to clarify, for example, whether the term "consultant" includes attorneys. It also asked if firms will have to document the qualifications of outside counsel. Under these regulations, a consultant is a person from outside the firm who is called on to render advice or opinion on current good manufacturing practice as it relates to the facilities or controls to be used in the manufacture, processing, packing, or holding of drug products.

The Commissioner believes this is generally well understood in the industry and sees no need to define "consultant" in these regulations. Any person, including attorneys, employed or retained to advise on the manufacture, processing, packing or holding of drug products would be considered a consultant under these regulations.

However, an attorney employed or retained for legal advice-- for example, an interpretation of CGMP regulations--would not be considered a consultant under these regulations. In response to the second part of the comment, the section requires that records be maintained stating the name, address, and qualifications of any consultant used.

IX. BUILDINGS AND FACILITIES

DESIGN AND CONSTRUCTION FEATURES

127. A number of comments suggested that the last sentence of 211.42(b), which deals with unnecessary traffic, is ambiguous. Two comments contend that the phrase "particularly movement back through areas in which these materials had previously been processed or held" be deleted as superfluous. The Commissioner is revising this paragraph to clarify the intended requirement that the flow of materials shall be designed to prevent contamination.

128. One comment proposed that under 211.42(c) the paragraph be divided into those operations which must be in defined areas and those which must be in separate areas. A number of comments regarding this section and 211.89 objected to a requirement that areas be set aside exclusively for quarantine storage.

The intent of this paragraph is to require that enough physical separation be employed as is necessary to prevent contamination or mixups. The degree of separation will depend on the type of operation and its proximity to other operations within the plant. The phrase "separate or defined" is not intended necessarily to mean a separate room or partitioned area, if other controls are adequate to prevent mixups and contamination. In the case of quarantined areas, for example, an effective means of identifying the quarantined goods and a paper control or other system may be used in lieu of complete physical separation.

Thus, the regulations do not require that space be reserved for quarantine storage. The Commissioner believes, however, that some degree of separation, even though only spatial, would be necessary in most cases, even with elaborate supplemental control.

129. One comment maintained that the quarantine of containers and closures involves a great deal of space which most small manufacturers do not have. The comment further contended that these items "can be examined at the packaging line just before use" or "can be examined at the distributor's facilities before shipment." If suitable specifications for containers and closures are simple enough to permit a quick visual examination to determine the product's acceptability, such an examination could be performed at the time of receipt without being in conflict with the quarantine requirements of these regulations.

A certificate of testing received from a supplier would not preclude the necessity for examining containers and closures to determine that they are the same articles as are represented by the certificate. Any manufacturer who does not have such evidence of an article's acceptability or does not alternatively quarantine the article until such evidence is obtained is assuming an unacceptable risk that the article will be used and subsequently be found unsuitable.

130. A number of comments indicated that the requirement in 211.42(c) that "operations shall be performed in specifically defined areas of adequate size" was unnecessarily restrictive on the flexibility of plant space use. The requirement relates to several different types of operations which are enumerated in the proposal; however, the comments seemed to relate mainly to storage areas.

It is the Commissioner's belief that a significant type of control over products is a physical one which precludes mixups by physically placing an article in an area clearly identified as to status. The extent of the physical separation imposed in a particular situation can vary from locked, walled-off areas to simple designation of an area for a single purpose by means of a sign.

The degree of physical control will vary depending on the other controls in use by a firm. If a firm has effective controls, whatever they may be, that would increase their confidence that mixups will not occur, then the degree of physical control may be less than in another firm where no other controls exist.

131. One comment contended that 211.42(c)(2) would require availability of a large separate holding area in the warehouse for relocation of rejected supplies. The Commissioner concludes that preventing the intermingling of rejected supplies with released supplies is very important to drug quality. The regulation does not require separate facilities as long as there is a defined area for rejected materials.

The Commissioner is not aware of any problems in the past with regard to large numbers of rejected supplies and their storage. He therefore rejects the proposal.

132. One comment objects to the requirement in 211.42(c)(4) for separate storage for "in-process" materials and suggests adding to this paragraph the words "if storage or isolation is necessary." The use of the word "storage" in this paragraph implies holding for extended periods of time. It does not refer to the holding of containers in production areas while processing is ongoing.

Therefore, if such storage is not necessary, the regulation as currently written is applicable. On the other hand, if such storage is necessary, it is the Commissioner's opinion that isolation in a separate or defined area is essential to prevent errors. Therefore, the comment's proposal is not accepted.

133. One comment, referring to 211.42(c)(5) said "on-line testing does not have to be done in a separate testing area ***."

The requirement is for separate or defined areas. The Commissioner believes that the area in which testing occurs,

including on-line testing, must be defined or separated in order to prevent contamination of on-line products with testing materials and improper use of products that have been tainted by the testing process.

134. One comment requested that 211.42(c)(5) be deleted since it is too broad to be helpful. The Commissioner disagrees with this comment. The intent of this paragraph is to avoid mixups by using defined areas for the entire manufacturing operation, phase-by-phase. The detailed procedures are purposely not spelled out so that pharmaceutical manufacturers can design their operations according to their individual needs.

135. Two comments argued that the word "quarantine" in 211.42(c)(7) is not defined, the word means different things to different people, and it should be deleted. The word "quarantine" has had widespread use in the pharmaceutical industry, and its meaning is well understood. These regulations do, however, have the effect of defining the word within the context of the pharmaceutical operations by indicating that it constitutes a control system to prevent unauthorized usage of unreleased material. The Commissioner does not believe further definition is necessary.

136. One comment argued that 211.42(c)(7) "increases warehouse requirements. This is not believed to be current practice in industry." Based on experience gained from FDA inspections of drug manufacturers, the Commissioner believes that most firms now separate released and unreleased drug products. In view of the intent of the phrase "separate or defined" as explained elsewhere in this preamble, the Commissioner concludes that 211.42(c)(7) and, similarly, 211.42(c)(8) reflect current industry practice and will not increase warehouse requirements.

137. A number of comments indicated that all the controls listed under 211.42(c)(10) are not needed in aseptic

processing areas for every product or process. One comment suggested that the term "aseptic processing" in 211.42(c)(10) requires further clarification to indicate that such processing is intended for products or components which are not terminally sterilized.

The respondents suggested inserting a phrase which would make it clear that not all controls are necessarily required. It is not the intent of 211.42(c)(10) to require "aseptic processing" when such operations would not be necessary for the firm's usual activities. Some firms choose to use aseptic processing for drug products not intended to be marketed as "sterile" as a means of controlling microbial contamination. The Commissioner agrees that modification is desirable and is revising 211.42(c)(10) to include the words "as appropriate."

138. One comment suggested that 211.42(c)(10) should be redesignated as paragraph (d) because it is unrelated to paragraph (c). These requirements relate to separate or defined areas for certain operations to prevent product contamination or mixups. The Commissioner concludes that such requirements are appropriately codified.

139. Several comments objected to the requirement under 211.42(c)(10)(i) that floors, walls, and ceilings have smooth, hard surfaces. The Commissioner rejects these comments. It is widely acknowledged that smooth, hard surfaces are easier to clean and sanitize.

140. A number of comments objected to applying the requirements of 121.42(d), 211.46(e), and 211.176 to the manufacturer of penicillin and nonpenicillin veterinary products. They claim that no evidence has been offered to demonstrate penicillin sensitivity in animals. It was proposed that the word "human" be inserted before the words "drug products." Hypersensitivity reactions to penicillin do occur in animals.

Although the Commissioner acknowledges that at present there is less information on the extent of the problem in animals than in humans, he advises that FDA has received numerous reports of reactions in animals throughout the years. Therefore, the Commissioner believes the requirement as proposed in 211.176 is warranted and has retained it in the final regulation. However, the Commissioner believes that the prohibition against the use of common facilities and air-handling systems in the production of veterinary drug products is not necessary at this time.

Therefore, 211.42(d) and 211.46(e) (now 211.46(d)) are revised accordingly in the final regulation.

141. A number of comments suggested that 211.42(d) can be too broadly construed. It was suggested that some processing steps for penicillin and nonpenicillin products could be performed on the same equipment without risk of cross-contamination. The Commissioner believes that there is a possibility of trace amounts of penicillin being released during product handling even under well-controlled conditions, and he therefore cannot accept this suggestion.

142. Another comment requested clarification of the meaning of the word "separate" in 211.42(d). The Commissioner's intent in this paragraph is to require the isolation of penicillin production operations from operations for nonpenicillin products. Separation can be achieved in a facility, building, or plant by effectively isolating and sealing off from one another these two types of operations.

This does not necessarily mean separation by geographical distance or the placement of these operations in separate buildings. Effective means can almost certainly be developed to separate such activities from one another to prevent cross-contamination problems within a single building. An example of the means of separation can be found in the discussion of air-handling systems in this preamble under paragraph 172.

LIGHTING

143. Two comments said 211.44 is vague and may lead to misinterpretation. It is not the intent of this section to spell out precisely what is required in the way of lighting for each type of operation, but rather to require that individual firms follow lighting standards that are generally considered adequate for each of their various operations. For example, inspection of parenteral solutions for particulate matter requires a different type of illumination than a component storage area. The Commissioner, therefore, has retained the proposed wording in the final regulation.

VENTILATION, AIR FILTRATION, AIR HEATING, AND COOLING

144. One comment suggested that the word "microorganisms" in 211.46(b) be modified by the term "objectionable." The Commissioner finds that this paragraph, by use of the phrases "adequate control" and "when appropriate," adequately states that the number or types of microorganisms that would be undesirable must be controlled. Therefore, the Commissioner has retained the wording as proposed in the final regulation.

145. A number of comments requested that expressions such as "when necessary," "where applicable," or "where appropriate" be used in the first sentence of 211.46(c) to broaden the scope of the requirement for air filtration systems. Comments took exception to the requirement for exhausting to the outside of the building, stating that there are a number of alternatives such as completely closed systems properly filtered, ionization and electrostatic precipitation, enclosed hoods, and scrubbers.

Finally, two comments contended that there is no reason for air filtration systems in production areas where the product is already in the final sealed container and in nonsterile processing areas. The Commissioner believes that for the great majority of drug production operations the proposed requirement is desirable and necessary to assure the quality of drug products. While it is doubtful that such air systems are not generally applicable to the production of nonsterile products, there may be situations where the requirement would not be necessary to assure the quality of drug products and would therefore be unreasonable.

Therefore, 211.46(c) is revised in the final regulation to require such filtration systems where appropriate. This paragraph as rewritten also allows alternative systems which do not necessarily exhaust outside the building.

146. Several comments objected to proposed 211.46(d) on the grounds that effective exhaust systems need not always be "adjacent" to the equipment in dusty operations. The Commissioner concludes that proposed 211.46(d) is unnecessary in view of 211.46(c) as written in the final regulation. Therefore, proposed 211.46(d) is deleted in its entirety.

147. One comment said proposed 211.46(e) (now 211.46(d)) is too general because there would be no danger from cross-contamination during penicillin fermentation (prior to processing the dry state) and after the sealing of the product. The Commissioner cannot agree with this comment since the operations specified are not clearly defined. He believes the fermentation process could result in cross-contamination problems.

For example, removal of the cake from penicillin fermentation equipment could result in airborne contamination from partly dry or dry cake. With regard to the respondent's second example, the Commissioner is revising this requirement to

make it apply only to production operations and not to storage, such as warehousing of the penicillin product in sealed containers.

148. Comments were made that proposed 211.46(e) was superfluous because 211.42(d) already required separate facilities for penicillin and nonpenicillin products. The Commissioner believes it is important to make clear in these regulations that completely separate air handling facilities for penicillin and nonpenicillin production are required. Section 211.42(d) is written to allow penicillin production in the same buildings as nonpenicillin production if the penicillin production areas can be completely separated from all others. However, because it is possible for air-handling systems between penicillin and nonpenicillin production areas to be interconnected, the Commissioner finds it necessary to state that any such interconnection would be unacceptable.

149. One comment said proposed 211.46(e) should specify whether the air-handling system is intended for outgoing or incoming air. There is no single answer to this point since the specific requirements for a particular installation will depend on individual circumstances. The purpose of the requirement is that no cross-contamination occur between penicillin and nonpenicillin operations.

The means by which the objective is achieved may require filtration of incoming air or filtration of outgoing air or both.

PLUMBING

150. A number of comments on 211.48(a) said water received from municipal sources and certified as meeting the requirements of Subpart J of 42 CFR Part 72 should not have to be tested as if it were another component. It was not the Commissioner's intent that potable water received from

municipal sources require acceptance testing by a drug manufacturer unless the water is obtained from sources that do not control the water quality to assure compliance with Public Health Service standards.

Of course, water of unknown quality such as a firm's own wells must be tested, and potable water coming into the plant system should not be adversely affected by the in-plant plumbing.

151. A number of comments indicated that it is not necessary and is very expensive to require that all water in a plant be potable water. They pointed out that some systems such as sprinklers for fire control, cooling equipment, and boiler feed do not require potable water. In light of these comments, the Commissioner is revising 211.48(a) to eliminate the prohibition against nonpotable water within a plant.

152. One comment said potable water should be analyzed for polychlorinated biphenyls and chloroform, and tolerances should be set because of the potential danger to health represented by these contaminants. The Commissioner recognizes that potable water may contain amounts of environmental chemical contaminants at levels that have not been clearly established as having significant adverse effects when ingested. Government agencies are investigating more meaningful specifications for testing potable water for potentially harmful impurities not already included in the standards. Therefore, FDA has not included such requirements for testing and acceptance of potable water in these regulations.

153. Several comments objected to the designation of traps to prevent back-siphonage in 211.48(b). The comments said it is general opinion that traps do not prevent back-siphonage, but check valves or air break arrangements would

do so. The Commissioner agrees with these comments, and 211.48(b) is revised to reflect the suggested change.

154. One comment objected to equipping drains with traps because of the inflationary impact and requested that this paragraph be deleted. The Commissioner notes that this paragraph is revised to eliminate the reference to traps. It now requires the use of air breaks or other mechanical device which may increase or decrease the cost to this person, depending on his present method of preventing back-siphonage. However, the Commissioner considers that the necessity of preventing back-siphonage outweighs the cost factor.

WASHING AND TOILET FACILITIES

155. Several comments on 211.52 argued that it is not current industry practice to provide "hot" water, but rather to provide "tempered" water, thus conserving energy while maintaining adequate sanitation facilities. The Commissioner has been unable determine that there is a consensus as to what is meant by "tempered water." Therefore, he is concerned that the word "tempered" might allow the use of water that is of insufficient temperature for adequate cleaning.

156. A comment suggested that the word "easily" be deleted from 211.52 because location of washing facilities may be hindered or prohibited by local plumbing codes. Further comment said the word "easily" is most subjective and capable of differing interpretation. The Commissioner is not convinced that plumbing codes would prohibit easily accessible washing facilities in establishments that are properly designed. Further, the Commissioner believes that the word "easily" is concise enough to adequately describe the intent of the section. Therefore, the wording as proposed is retained in the final regulation.

ANIMAL FACILITIES

157. Several comments contended that proposed 211.54 should be deleted since its substance is covered by the Animal Welfare Act of 1970 (Pub. L. 91-579, 7 U.S.C. 2131). Other comments said this section implies that housing for laboratory animals is required whether or not a firm maintains laboratory animals. The Commissioner does not believe it is improper to make the substance of another regulation a requirement in the CGMP regulations.

It should be obvious that if a firm is not engaged in a type of operation covered by these regulations, then any requirement that pertains to that type of operation does not apply to that firm. In reviewing this proposed section, however, the Commissioner has concluded that its intent is adequately covered in 211.173. Therefore, 211.54 is deleted in the final regulation.

SANITATION

158. Several comments on 211.56(a) said it is impossible to maintain all buildings completely free from rodents, birds, insects, vermin, trash, and organic decaying matter. In most buildings there is an accumulation of trash daily in various waste baskets and in trash accumulation areas for papers and empty cartons. The Commissioner agrees that the intent of this section could be more clearly stated, and the text is revised accordingly.

159. Several comments requested the deletion of the phrase "in detail" from 211.56(b), because, according to the language in this paragraph, manufacturers would be required to document all minute details. The Commissioner believes that in some cases, detailed descriptions of cleaning procedures may be necessary to assure complete and proper cleaning. In others, that level of detail may not be necessary or appropriate. The Commissioner believes that there should

be a reasonable standard in describing the details of these procedures. Therefore, this paragraph is revised to require "sufficient" detail.

160. Several comments requested the deletion of the phrase "such written procedures shall be followed" from 211.56(b) because, if current good manufacturing practice involves writing down certain procedures, it also involves following them.

The Commissioner does not agree with this comment. Procedures may be written with obvious good intentions but never implemented, as the agency has discovered in some firms. Written procedures must be followed to assure the quality of finished drug product, and the regulations should be explicit in stating this point.

161. Comments regarding 211.56(c) objected to the use of the word "person" and to the requirement of "evidence" that use of such materials will not contaminate equipment, components, or in-process materials. The use of the word "person" according to the comments seems to have a more personal use here than the general use it has in other sections.

It was also suggested that the word "evidence" implied a need for proof of lack of any residue from pesticide or cleaning agent use, and that the standard should be a lack of adverse effect instead. Several comments suggested that as written, this paragraph would require residue checks to be run on all batches in an area after a visit by an exterminator.

The Commissioner finds that the objections have merit, and therefore the opening of this paragraph is reworded to clarify the intent. It is not the intent of the Commissioner to burden manufacturers with testing every batch of drug product in a particular area for contamination from chemicals used to kill pests and insects.

162. Several comments requested the deletion of the last sentence of 211.56(c), which allows the use of only those rodenticides, insecticides, and fungicides that have been registered in accordance with the Federal Insecticide, Fungicide and Rodenticide Act (7 U.S.C. 135). The Commissioner believes it contrary to public policy to permit the use of unregistered rodenticides, insecticides, or fungicides. The comment is rejected.

163. One comment requested insertion of the phrase "employed to perform sanitation work" following the word "employees" in 211.56(d) to clarify that the procedures apply to individuals who are assigned to sanitation work. The Commissioner believes that the paragraph clearly indicates that good sanitation procedures apply to all employees who perform sanitation work. Therefore, he rejects this comment.

MAINTENANCE

164. Several comments said the phrase "good state of repair" in 211.58 is vague and is subject to varying interpretation. The Commissioner does not agree that the phrase "good state of repair" is vague. It means that buildings should not be in a bad state of repair so that drug products processed within them are adversely affected.

X. EQUIPMENT

EQUIPMENT DESIGN, SIZE AND LOCATION

165. A comment suggested the deletion of the phrase in 211.63 "for its intended use as well as for its" on the grounds that it is redundant and therefore unnecessary. The Commissioner does not agree that this phrase is redundant. The regulation imposes two requirements: that equipment be such as to facilitate its operations for its intended use and that equipment be such as to facilitate its cleaning and maintenance. The phrase is revised in the final regulations for clarity.

166. One comment on 211.63 noted that medical gas manufacturers use dedicated piping systems, manifold valve outlets, and pin index systems for processing medical gases. Cleaning except at the time of initial installation and subsequent maintenance, is not done internally. The Commissioner notes that this section does not dictate the frequency of cleaning and/or maintenance. If cleaning and maintenance after initial installation are not needed, as stated in the comment, then there is no requirement in 211.63 for such practice.

EQUIPMENT CONSTRUCTION

167. A number of comments argued that 211.65(a) literally requires that all product contact surfaces be totally inert. The respondents maintained that this requirement is practically impossible to achieve and that the following wording should be added: "* * * so as to alter the safety, identity, strength, quality or purity of the drug beyond the official or other established requirements."

The Commissioner recognizes that drug product contact surfaces may be reactive to some minute extent, and the

paragraph is revised in the final regulation in accordance with suggested alternative wording.

168. A number of comments suggested adding the phrase "beyond the official or other established requirements" to the end of 211.65(b) to define better the standards to be used for evaluating any possible changes caused by product contacts. The Commissioner agrees with the substance of these comments. The proposed phrase is added at the end of the sentence in 211.65(b) for the same reason as explained in reference to 211.65(a). A similar change is made in 211.67(a).

EQUIPMENT CLEANING AND MAINTENANCE

169. In reviewing the proposed regulations the Commissioner concludes that 211.67 and 211.112 should be combined into a new 211.67. Section 211.112 is deleted from the final regulation, and the substance of the requirements in proposed 211.112 are included in the new 211.67. The comments below include those relating to both proposed 211.67 and 211.112.

170. Several comments said written procedures and documentation required by 211.67 should apply only to major equipment, not to items such as ladles, buckets, and spatulas.

The Commissioner does not necessarily intend to require detailed procedures for cleaning each type of utensil. For example, such equipment may be grouped when convenient. However, the Commissioner believes that at least general written procedures should be instituted for cleaning utensils. Although not "major" pieces of equipment, utensils can be just as much a source of contamination. Depending on the type of operation, it may be necessary, for example, to sanitize or use procedures other than simple washing.

171. One comment said 211.67 should be strengthened by requiring that cleaning and identification be performed by a competent individual specifically trained for these operations. The Commissioner rejects this comment because it would be repetitive of the requirements in 211.25 on personnel qualifications.

172. One comment on 211.67(a) said that when equipment is dedicated to a single component or product, the use of water solution or gas purging would serve only to introduce material which should not be in the final product.

This paragraph does not prescribe what compounds must be used for cleaning, the manner, or the exact frequency of cleaning. To do so would be impossible, given the variety of products, equipment, manufacturing operations, and cleaning techniques. Selection is best left to each manufacturer, who also retains responsibility for assuring that their cleaning operations do not contaminate the drug product.

173. One comment said the list of procedural requirements for equipment cleaning should be deleted from 211.112(a) since it is unnecessarily specific and unduly restrictive. The Commissioner does not agree that the list of required procedures is either too restrictive or too specific. He believes that all the items are common sense procedures that most firms would incorporate, but some would not in the absence of CGMP regulations.

174. One comment on proposed 211.112 argued that the word "shall" in the sentence regarding establishment of procedures should be replaced by the word "may" because the judgment of the manufacturing personnel should determine proper sanitary procedures. The Commissioner rejects this suggestion. The purpose of these regulations is to assure that each firm establish appropriate written procedures regarding sanitation. Precise procedures are left to the reasonable

judgment of manufacturing personnel, as long as the objectives of the requirement are met.

175. One comment said that 211.67 as written requires the cleaning and maintenance of all equipment used in the manufacture, processing, packing, and holding of a drug product, which would include laboratory equipment, fork lifts, and truck fleets. Any equipment used in association with drug manufacturing that could have an adverse effect on drug product quality if improperly maintained is covered by this section.

Ordinarily, of course, fork lifts and fleet trucks would not be considered, but it is not inconceivable, for example, that the failure of a refrigeration unit in a truck could have a serious deleterious effect on drug products that must be kept cool. Laboratory equipment, when used for the quality control of drug products, is an integral part of the manufacture, processing, packing, or holding of drug products and therefore clearly is included in the scope of 211.67. 176. Several comments on 211.67 argued that requiring written procedures for the method used in the disassembling and reassembling of all equipment is overly burdensome and not necessary. It was recommended that the paragraph be deleted or rewritten to require such measures for significant pieces of equipment only. It was also recommended that parts which come into contact with drug products be disassembled, cleaned and reassembled, but not necessarily the entire piece of equipment.

The Commissioner concludes that the extent to which equipment must be disassembled depends on the type of equipment and other variable factors. The equipment must be disassembled to the extent necessary to prevent subsequent contamination and/or malfunction. The regulations in 211.67(b)(3) are clarified in this regard.

177. Several comments said 211.67(b) would require written procedures for "maintenance" of equipment and objected that the word "maintenance" is too general a term.

One comment recommended that the paragraph be revised to read, "There shall be written procedures assigning responsibility for and describing preventive maintenance programs and cleaning schedules." The Commissioner does not agree that rewording the paragraph, as suggested, is necessary. Maintenance means keeping a building, machinery, or other facilities in a good state of repair; and the term is understood throughout the industry.

178. One comment said 211.67(b) is not relevant to good manufacturing practice for most products. The comment further said the description of the methods of disassembling, cleaning, and sterilizing is applicable only to parenteral drugs. The Commissioner does not agree with this comment. Other types of equipment, for example, automatic tableting machines, also require disassembling, cleaning, and reassembling.

179. Several comments requested that the phrase "such written procedures shall be followed" be deleted from 211.67(b). The Commissioner does not agree with this comment. The requirement for written procedures is only part of the requirement for the use of current good manufacturing practice in the production of drugs. An equally critical part of the requirement is that the written procedures be followed.

180. One comment objected to the requirement in 211.67(c) for making the maintenance and cleaning records a part of the equipment use log (as required in 211.182) because the information is readily available in batch records. The Commissioner rejects this comment. The intent of the record retention requirement is that cleaning and maintenance records be readily identifiable with equipment usage in the event of a problem where drug products must be investigated.

Where the same equipment is used for a number of different drug products, for example, cleaning and maintenance records may not be easily retrieved.

Section 211.182 in the final regulations provides, however, that individual equipment logs are not required where equipment is dedicated to the manufacture of one product and the batches are manufactured in numerical sequence. 181. Several comments requested the deletion from proposed 211.67(c) and 211.112(a)(6) of the references to 211.180 and 211.182 with regard to the record retention period.

The Commissioner disagrees with these comments. Section 211.182 provides the specific information and form in which equipment usage, cleaning, and maintenance records must be kept and is appropriate so that firms subject to these regulations are made aware of their responsibilities. Further, improper cleaning and sanitizing could contribute as significantly to adulteration of products as could other problems in the manufacturing process and, in the event of contaminated products, the firm should be able to identify the cause of the contamination.

The retention of these records under 211.180 therefore should be consistent with other recordkeeping requirements throughout the CGMP regulations.

EQUIPMENT CALIBRATION

182. The Commissioner is combining the substantive requirements of proposed 211.2 and 211.68 to form new 211.68. Comments on proposed 211.2 and 211.68 will be discussed here.

183. One comment requested that proposed 211.2(a) be modified to permit the use of equipment other than the types listed. One comment argued that the use of computers should be allowed. Several comments suggested deletion of

the word "precision" since it is superfluous and redundant. The intent of this paragraph is to allow the use of any equipment that will perform a function satisfactorily in accordance with the requirements in Part 211.

The Commissioner is therefore revising this paragraph in the final regulation (now 211.68(a)) to permit the use of any automatic, mechanical, electronic, or other types of equipment, including computers or related systems, that will achieve this goal. Use of modifying word "precision" is not necessary because the paragraph requires that any equipment perform a function satisfactorily.

184. One comment suggested that the word "permit" in 211.2(a) be replaced by the word "recognize," which would better express the intent of the paragraph. Several comments questioned the statutory authority of FDA to permit or prohibit the use of specific types or classes of equipment. The revision of proposed 211.2(a) (now 211.68(a)) eliminates the word "permit."

The authority to promulgate CGMP regulations includes the authority to regulate the use of equipment that could have a bearing on drug product quality. The argument that FDA does not have the authority to prohibit the use of equipment is academic, however, because there is no prohibition stated or implied. Testing and quality control are an inherent part of the manufacture, processing, packaging, and holding of drug products as defined in 210.3(b)(12). Therefore, such equipment may also be used for testing and quality control.

185. Numerous comments suggested that the requirement in proposed 211.2(b) for a backup file of hard copy data be amended to provide for other types of backup data, such as duplicate tapes or microfilm. The Commissioner is convinced that it would be proper to allow for backup systems other than hard copy, and this paragraph is revised accordingly as 211.68(b). Measures must be taken, however,

to assure that backup data are exact and complete and that they are secure from alteration, inadvertent erasure, and loss.

186. Several comments objected to the requirement in proposed 211.2(b) for checking computer reproductions of formulas and other records or data each time they are used, on the grounds that it should be sufficient to verify only the accuracy of the first reproduction. The intent of this requirement is to ensure that each reproduction is the same as the original. Computer printouts do, on occasion, contain errors. Whether due to faulty input, programming, malfunction, or other reasons, they can result in a serious production error and the distribution of an adulterated product.

The Commissioner therefore does not agree that only the first reproduction need be checked for accuracy. If a computer system has the capability, however, to verify its output, such as with audit trials, this could be considered as a check for accuracy.

187. One comment suggested deletion from proposed 211.2(b) of the listing of items requiring backup data. The Commissioner now believes that the listing of data to be included as hard copy data is not necessary. The intent of this paragraph is that backup data be kept of any information that is computerized, not that certain information be computerized.

188. One comment suggested deletion of the word "appropriate" in the second sentence of proposed 211.2(b), charging it to be superfluous. The Commissioner rejects this suggestion. Controls required by this paragraph must be adequate to achieve their purpose, but are not required to exceed this level.

189. One comment suggested that the third sentence of proposed 211.2(b) be modified by deleting the word "reproductions" and replacing it with the phrase "input to the computer." The comment also suggested deletion of the

phrase "data from the computer." The Commissioner agrees that input to the computer must be checked for accuracy and is revising the paragraph accordingly in 211.68(b). He does not agree that "data from the computer" need not be checked for accuracy and therefore rejects that portion of the comment.

In considering the comments on the section and as a result of discussions with FDA staff knowledgeable in the computer field, the Commissioner has become aware that use of the word "computer" may be too restrictive so as to exclude data processing systems that do not compute. Therefore, the words "related systems" are added to include those systems that function only as data storage and retrieval.

190. One comment on 211.68(a) asked whether electronic equipment recorders should be calibrated. The Commissioner believes that recorders are an integral part of precision equipment systems. A faulty recorder may give unreliable results that may affect the quality of finished drug products. Recorders that are routinely calibrated, inspected, and checked reduce the margin for error and assure the quality of drug products.

191. A comment said the intent of 211.68(a) is not clear as to the use and type of equipment that is applicable. The comment further said precision equipment that has no effect on the drug product quality should be exempted from the written program requirements. The paragraph refers to equipment which is used in the manufacture, processing, packing, and holding of drugs and may therefore have an effect on drug product quality. No examples of equipment which did not have an effect on drug product quality were offered.

192. A comment requested that the term "precision automatic equipment" be defined. The respondent said it could, for example, include tablet counters and liquid fillers

which are checked on a routine in-process basis where there is no need for routine calibration or inspection.

The Commissioner believes that tablet counters and liquid fillers are examples of precision automatic equipment. When routing in-process checks are made, regardless of the time interval, such checks should be performed according to prescribed procedures and records kept in accordance with the requirements of this paragraph.

193. Several comments on 211.68(b) said the mandatory time interval of 6 months for calibration checks on scales and balances is arbitrary. The Commissioner agrees that time intervals longer than 6 months may be appropriate in some cases. Because 211.68(a) requires that automatic, mechanical, and electronic equipment, including scales and balances, be calibrated routinely to assure the quality of drug products, the provisions of 211.68(b) are unnecessary and therefore are deleted.

193a. A comment requested the insertion of the word "weight" before the word "scales" in 211.68(b) to clarify that this requirement applies only to weight scales. The deletion of 211.68(b), as proposed, removes the reference to "weight"; however, the Commissioner finds that any scale or balance used for testing of production operations is required to be accurate and must be calibrated and checked routinely as required in 211.68(a).

194. A comment requested an additional paragraph covering the standardization of tablet punch and die sets. Although the Commissioner believes that the comment has merit, he does not believe that it is generally appropriate in a general set of regulations to identify specific equipment used only in the manufacturing of one dosage form. Such requirements are more appropriate in regulations for specific dosage forms.

FILTERS

195. A number of comments on 211.72 requested clarification whether this section is intended to apply to both air filters and solution filters. Other comments requested clarification that the proposed paragraphs (b) and (c) refer only to injectable drug products intended for human use. The Commissioner finds that the intent of this section is to eliminate the use of fiber-releasing filters in liquid filtration systems during production of injectable drug products for human use. Revisions appearing in the final regulation clarify this intent.

Additional background information regarding this requirement can be found in the FEDERAL REGISTER of March 14, 1975 (40 FR 11865), which established the basic requirements for this section.

196. Several comments suggested that this section be deleted because it pertains only to injectable drug products and therefore should be placed in the specific regulations for this type of drug product. The Commissioner agrees that this section and a portion of 211.94 apply only to injectable drug products for human use and that such requirements will be suitable for the more specific regulations for large and small volume parenterals for human use when such regulations are in effect.

The Commissioner previously concluded in the final regulation published in the FEDERAL REGISTER of March 14, 1975 (40 FR 11865) that the use of fiber-releasing filters in the production of human injectables required codification in the general CGMP regulations until final LVP and SVP CGMP regulations are codified. These provisions will be incorporated in the more specific regulations regarding human parenteral drug products when they are published as final regulations. Again, the Commissioner reminds interested persons that this section has been in effect since April 14, 1975 (40 FR 11865).

197. One comment noted that by the time the final regulation becomes effective, proposed 211.72(c) will be inoperative, since it requires substitution on or before September 14, 1976. The Commissioner agrees with this comment and is therefore deleting paragraph (c) of 211.72.

198. One comment objected to being forced to use filters in drug production. Section 211.72 does not require the use of filters in the manufacture, processing, or packing of injectable drug products. However, if filters are used, 211.72 specifies types of filters that cannot be used unless the drug product cannot be manufactured, processed, or packed without their use, and also requires that in this eventuality the drug product be refiltered through a nonfiber-releasing filter.

XI. CONTROL OF COMPONENTS AND DRUG PRODUCT CONTAINERS AND CLOSURES

GENERAL REQUIREMENTS

199. Several comments suggested that the requirements for containers and closures in proposed 211.80(a) and 211.89 be separated from those for components and in-process materials because the testing controls, systems, and criteria differ. The Commissioner finds that the control of in-process materials is more appropriate in Subpart F-Production Process Controls; therefore, all references in Subpart E to in-process materials are deleted. Proposed 211.88 and certain requirements proposed in 211.89 are now in 211.110(c) and (d).

It is appropriate to consider control of components, drug product containers, and closures together, however, because the separation of requirements for control of containers and closures from components in the CGMP regulations would necessitate the unwarranted duplication of numerous sections of text. The variations in handling, examining, or testing can be adequately addressed by each manufacturer in the written procedures required by the various sections.

200. One comment argued that these proposed requirements in Subpart E would place an additional burden on small manufacturers and that such requirements are unnecessary, particularly with OTC pharmaceuticals. Drug product containers and closures play a critical role in assuring that the patient is provided a drug product of essentially the same strength, quality, and purity as when it was produced by the manufacturer.

The Commissioner cannot agree that OTC drug products should not receive the same degree of protection as prescription drug products. It has been FDA's experience that "small" manufacturers can attain the same degree of quality of

their drug products as large manufacturers. There cannot be different standards of quality of drug products for large and small manufacturers, nor can there be different standards of quality for OTC and prescription drug products.

201. One comment on 211.80(a) raised several issues relative to the handling of bulk components being held in storage tanks or silos, including the commingling of a new shipment with the remainder from previous shipments and how such lots should be identified.

Combining a new bulk shipment of a component in a bulk storage tank with the remainder of a previously received, tested, and approved component lot causes the compositing of the material. The result is that the previously approved material becomes an integral part of an unapproved new lot and cannot be used until such lot is approved for use.

However, a manufacturer may choose not to commingle approved lots with unapproved lots of components in bulk storage. In some instances a manufacturer may be able to test components appropriately before introduction to bulk storage as, for example, when a shipment of components is received with a valid certificate of analysis and where identification testing may be sufficient.

202. Some comments suggested deletion from 211.80(a) of the words "in detail" because it would require the documentation of minutiae and voluminous written procedures. The Commissioner agrees that the phrase "in detail" could be construed to include description of insignificant portions of the procedure, which is not the intent. Therefore, he is inserting the word "sufficient" before the word "detail."

203. Comments were received on 211.80(a) recommending replacement of the phrase "approval or rejection" with the word "disposition." The Commissioner disagrees with this suggestion. Written procedures must spell

out the criteria for approval or rejection in view of such material's intended use.

204. One comment suggested that the first sentence of 211.80(a) be preceded by the phrase "where appropriate" to allow for the size and complexity of the operation. The Commissioner believes that written procedures are appropriate regardless of the size or complexity of the operation. Written procedures provide a basis for the uniform performance of a function.

205. One comment suggested adding to 211.80(b) the phrase "so as to alter the safety or efficacy of the drug product." The Commissioner finds that it is reasonable to conclude that contamination would affect drug quality. Therefore, the suggested phrase is unnecessary and is not included in the final regulations.

206. Numerous comments strongly objected to the requirement in 211.80(c) that components, drug product containers, or closures be stored at least 2 feet away from walls, maintaining that it would severely reduce the available storage area and thereby necessitate additional space to store the amount of material with an attendant inordinate and unnecessary inflationary impact. Some of these comments suggested that this sanitation-oriented requirement be placed in 211.56 or combined with 211.80(b).

Additionally, some comments offered alternate wording such as: to permit cleaning and inspection, to allow for appropriate sanitation operations, and to allow for effective sanitation practice. Some comments questioned whether this requirement only refers to outside walls or includes all walls, such as mesh screened walls, vault walls, partitions, and refrigerator and freezer walls.

Some comments questioned whether free-standing shelves also had to be "at least 2 feet away from walls," since shelving

is sometimes attached to the wall for safety reasons. The Commissioner has carefully evaluated this paragraph in light of his intention to provide suitable spacing in storage areas for cleaning and inspection and concludes that a specific requirement for at least 2-foot space between the wall and such material can be deleted, but a requirement to store materials in a way that allows for cleaning and inspection will be retained. He is also deleting the words "on pallets or free standing shelves" to allow for other suitable methods of storage.

The Commissioner believes it preferable to codify this requirement in this section rather than in 211.56. 207. Numerous comments on 211.80(d) objected to the proposed requirement to identify each container in a lot being received since many items, such as containers, closures, and excipients are palletized. This requirement, as proposed, would mandate that each pallet load be broken down so that each unit on the pallet could be identified, then repalletized, thereby increasing the potential for damage and mixups.

This procedure is alleged to have an unnecessary inflationary impact. The Commissioner recognizes that there are situations where it would be inappropriate to identify each container of component, drug product container, or closure such as mentioned in the proposed regulation. He agrees that some provision should be made for these situations.

He is therefore amending this paragraph by adding the words "or grouping of containers." Any individual unit separated from a grouping must be identified with the appropriate information required by this paragraph.

208. Some comments requested a clarification of the word "disposition" in 211.80(d) that would distinguish between a simple transfer of the material and use of the material for a particular purpose. The Commissioner believes that the word

"disposition" appropriately covers any use or change in control status of the lot, including both those cited in the comments.

209. Some comments questioned the intent of the last phrase of 211.80(d). The respondents stated that if the intent is to identify those containers that have been opened, then a period should be placed after the parentheses and a suggested new sentence added to clarify the intent. The Commissioner agrees that this phrase could be interpreted to require that only the lot be marked to indicate whether and when it had been opened and sampled.

The requirement for the sampling of lots is contained in 211.84. Therefore, he concludes that the requirement in 211.80(d) regarding identifying sampled containers is more appropriately placed in 211.84(c), which will clarify the intent to identify containers which have been sampled.

210. One comment on 211.80(d) suggested that when a shipment of components contains more than one manufacturer's lot number, the recipient be allowed the option of assigning a single code number for this shipment. The Commissioner rejects this suggestion inasmuch as it would either complicate or negate tracing a component back to a particular manufacturer's lot or the subsequent tracing of a particular lot of component used to a lot of drug products.

211. One comment objected to the requirement in 211.80(d) that containers of drug product containers bear an identifiable lot number, on the grounds that this is not standard practice in the industry. The comment suggested that the recipient provide a distinctive code for such containers. The requirement is that each lot of each shipment be identified with a distinctive code. If a lot number furnished by the supplier is distinctive for each lot in each shipment, then the recipient, i.e., the drug product manufacturer, can use the lot number as the distinctive code.

If, however, there is no lot number or the lot number is not distinctive for each lot in each shipment, then the recipient is responsible for designating his own distinctive code.

RECEIPT AND STORAGE OF UNTESTED COMPONENTS, DRUG PRODUCT CONTAINERS, AND CLOSURES

212. One comment proposed that 211.82(a) be divided to cover components, and containers and closures separately. The identification of articles received, comparison with materials ordered, and examination of the overall condition of the material received is carried out in much the same way regardless of the character of the article received. The Commissioner sees no advantage to promulgating two separate regulations on receiving and storage of materials, one for components, and the other for containers and closures. To do so would simply be redundant.

213. A number of comments on 211.82(a) said individual containers of components, containers, and closures need not be visually examined before acceptance as long as they are checked before use. The rationale for the comments is that a visual check of each container is impractical and unrealistic for large shipments of bagged materials that are palletized as a unit and/or shrink-wrapped.

The respondents suggested that tearing apart materials packaged in that manner would be costly and could be better done before use rather than in a receiving area. It was the Commissioner's intent in this paragraph to provide for a simple check at the time of receipt to detect obvious problems such as the wrong article, damaged containers, or visible contamination which would preclude any further handling of the materials. He recognizes, however, that individual container examination of large lots of bagged or boxed materials is impractical when they are received. Therefore, this requirement is revised to provide for examination of each container or grouping of containers.

214. A number of comments expressed concern over the possibility of contamination if containers of components and other materials are opened for examination in the receiving areas of factories. To avoid cross-contamination it was suggested that examinations be limited to the exterior of the containers or to shipping containers.

The Commissioner notes that this paragraph does not specify that seals must be broken for purposes of examination. It is the intent of this paragraph that a visual examination be performed. In most cases it would be adequate to limit the examination to shipping containers. If the firm feels an inspection should be made in depth, proper precautions must be taken to prevent cross-contamination.

215. Several comments in regard to 211.82(b) objected to the concept of setting a special area aside for quarantined materials. They felt that reserving space for this purpose and moving stock into and out of this special quarantine area would be costly because of the additional space and labor required. Further, some felt that paperwork systems can accomplish quarantine purposes.

The Commissioner refers to the detailed discussion in paragraph 128 of this preamble that describes the variety and degree of physical quarantine procedures which, when combined with other controls, provide the assurance necessary to prevent untested and unreleased materials from being used in drug manufacturing operations.

216. Several comments on 211.82(b) and 211.84(a) proposed that components should be "tested" whereas containers and closures should be "examined visually," and that the word "tested" should be deleted whenever it refers to containers and closures. The Commissioner does not agree that appropriate testing of containers and closures can be limited in all cases to visual examination.

Even in instances where visual examination would suffice, however, the word "testing" is meant to include such examination. Other CGMP regulations do use the word "examination" along with "testing" to suggest a lesser type of testing, if appropriate, however; and the Commissioner is therefore adding the phrase "or examined, as appropriate" to prevent any misinterpretation of 211.82(b) and 211.84(a).

TESTING AND APPROVAL OR REJECTION OF COMPONENTS, DRUG PRODUCT CONTAINERS, AND CLOSURES

217. Citing various reasons, comments suggested that 211.84(a) be revised to permit use of components, drug product containers, and closures, simultaneously with testing and with precautions to prevent release of the drug product until the tests indicate compliance with specifications. As a general principle, such procedures would violate the precepts of good quality control because untested and possibly noncomplying materials would be used in drug product processing.

Although initially it would appear that the manufacturer merely assumes the risk of having to recondition or destroy a processed lot that was found to contain unsatisfactory components, containers, or closures, the Commissioner is concerned that processing while testing substantially increases the risk to the consumer that an unsatisfactory lot might erroneously be released. The Commissioner cannot accept such risks or these suggestions.

218. Two comments on 211.84 suggested that the only practical test of product container and closure acceptability is the actual use of them. The Commissioner rejects the concept. He notes that there are techniques available and in use by which the suitability of a container-closure system can be determined before its use.

Manufacturers do develop specifications for product acceptance when making their purchases. Such purchases are made with definite knowledge of what is needed. The regulation simply requires that checks be made to assure that what has been received is what has been ordered.

219. One comment suggested that a protocol or certificate from the container manufacturer that the container meets the U.S.P. requirements be acceptable in lieu of the recipient performing the tests. The Commissioner notes that certificates or reports of analysis are acceptable for components with certain provisions, such as periodical verification of the supplier's test results.

Therefore, he would have no reservation about accepting a certificate or report of analysis with each shipment of drug product containers--as long as the lot of containers is appropriately identified, the supplier's results are periodically verified, and their certificate provides all appropriate testing. A new paragraph, 211.184(d)(3), is added to clarify this provision.

220. One comment interpreted 211.84(a) to require that each lot of components, drug product containers, and closures be tested before each use in processing. This paragraph does not require such a practice, nor is that intended. 221. Several comments questioned the meaning of container identification in 211.84(a) and its relationship to a similar requirement in 211.80. The Commissioner is deleting the requirement regarding container identification from 211.84(a) because such requirement more appropriately appears in 211.80. 222.

Several veterinary drug manufacturers responded that the testing requirements for drug product containers and closures in 211.84(a) should not apply to veterinary drugs or that a very simple visual examination of such items would be all that is necessary for animal products. One comment said the

requirements for containers and closures in Subpart E are not current good manufacturing practice for the veterinary drug industry. The Commissioner does not accept the stated premise that the veterinary drug industry does not exercise such control over these containers and closures to ensure the protection of their drug products from external influences such as light, moisture, and microbes.

The agency's experience in inspecting veterinary drug manufacturers and in reviewing new animal drug applications indicates that this is not so. The requirements of Subpart E can and should apply to both human and veterinary drug products.

223. A number of comments on 211.84(b) objected to a requirement for the use of statistical criteria to determine the sample sizes for testing. Many of the comments recommended that the requirement be made optional or that it be applied only when necessary or appropriate. Some suggested that few people in the pharmaceutical industry understand statistical methods and that even experts differ on interpretation and application.

One comment suggested that representative samples are impossible for all materials and suggested that random, sampling be permitted. The Commissioner believes that statistical methods provide a rational basis for determining sample sizes, provide assurance that an adequate sample has been obtained, and increase the user's confidence that the results from testing of the sample are representative of the true conditions of the product sampled.

The Commissioner recognizes, however, that other sampling plans, derived by other means, may also be adequate, and this section is revised to allow the use of alternative types of sampling plans. This will allow for use of random sampling methods if appropriate.

224. A few comments requested that containers and closures not be included in the representative sample requirement of 211.84(b). No rationale was included to explain the request. If the comments meant that other sampling methods such as random sampling are more appropriate, then the change made in this paragraph will be responsive to these comments. If the comments meant that containers and closures should not be sampled at all, the Commissioner rejects the comments because he believes that examinations must be made on product containers and closures to assure their suitability for use in drug product packaging.

225. One comment requested explanation of an acceptable "past quality history of a supplier," as suggested by 211.84(b). The Commissioner did not use the word "acceptable" in his proposal, but did permit the past quality history to be used in determining sampling plans for articles received from various suppliers.

The object of considering the past quality history is that the fewer the problems encountered with materials from a particular supplier and the more often that supplier's products meet specifications, the less extensive the sampling schedule may need to be for that material. Conversely, the more problems encountered with articles from a particular supplier, the more extensive the sampling schedules for the articles need to be.

226. One comment suggested that the word "incoming" be inserted before the word "shipment" so that the sentence is clear that no reference is being made to outgoing shipments. The Commissioner believes the meaning of the section is clear and that the sentence refers to materials received for use in drug production. Therefore, no change is made in the final regulation.

227. One comment suggested deletion of the reserve requirement in 211.84(b) because such a requirement appears

in 211.170(a) and is appropriate only for components. To clarify his intent here, the Commissioner is adding the words "where required by 211.170."

228. Two comments recommended that the requirement in 211.84(b) for testing each shipment of each lot is unnecessary when a previous shipment of the same lot had been received, tested, and approved. The Commissioner feels that examination of each lot of each shipment received is necessary even though a portion of the same lot has previously been received, tested, and approved.

Subsequent shipments may have been subjected to different conditions which may have caused changes in materials so that, although one shipment of a particular lot has met specifications, another may not.

229. Fifteen comments on 211.84(c)(1) stated that containers from which samples are being collected do not always need to be wiped or vacuumed. In addition, two other comments requested deletion of all the paragraphs as unnecessary because all manufacturers know what they need to do. The Commissioner agrees that a container of components may not always need cleaning before sampling and that, where cleaning is needed, wiping or vacuuming may not necessarily be the most effective means of cleaning.

Therefore, he is revising 211.84(c)(1) to provide manufacturers with more latitude in this operation. The Commissioner does not agree, however, that controls used in sampling are uniform throughout the pharmaceutical industry. Some manufacturers already have the controls required here, while others do not. Therefore, this requirement is appropriate in the CGMP regulations.

230. Several comments suggested inclusion of additional controls in this section as follows: provisions for handling sterile materials; a requirement that each container

that is sampled be marked; and identification of the location within a container from which a sample was taken. The Commissioner believes that the proposed requirements, with one exception, provide sufficient control of sampling procedures.

The language of this section is general to allow for a wide variety of methods of handling products with a wide variety of characteristics. It is not the Commissioner's intent to design a specific control procedure which a manufacturer must follow, or to preclude flexibility in meeting this objective. It is sufficient here to state the control desired and leave the specifics to the reasonable judgment of the manufacturer.

The Commissioner believes that the suggestion for identifying the locations within a container where samples have been taken is inherent in 211.84. To clarify that containers from which samples are taken must be marked in order to produce an appropriate record, the Commissioner is adding a new 211.84(c)(6).

231. A number of comments were received on 211.84(c)(4) relating to component subsampling and compositing of subsamples. The majority of those commenting recommended that the regulations allow for compositing. Some respondents stated that sampling at multiple levels is not always necessary. Others suggested that the instances be spelled out where sampling at multiple levels is necessary.

One comment indicated that compositing is a satisfactory procedure if the container contents are all going to be used in a single drug product lot. The intent of this proposed section is to prohibit the compositing of samples taken from different portions of a container when there is a possibility that the composition of the material being sampled may vary within the container.

There is no general prohibition in the regulations on compositing samples where such compositing would not mask subdivisions of the sample that do not meet specifications.

232. A number of comments suggested changes in the requirements proposed in 211.84(c)(5) for identifying the sample containers. Three comments objected to the proposed sample container identification as being too burdensome because the information is available in other documents. One comment suggested that an in-house code to identify samples is adequate. Another said that the proposed sample container identification is not a current good manufacturing practice.

It is not the Commissioner's intent that all the listed information appear on the sample container. Section 211.84(c)(5) is reworded to require only a means whereby sample containers can be related to the required identification information.

233. One respondent expressed concern that the requirement for opening containers for sampling in a suitable area would lead to separate areas for each ingredient. This paragraph is revised in the final regulation, and the words "suitable area" are deleted.

234. One comment suggested deletion of the word "containers" in 211.84(c)(2) dealing with cross-contamination because the requirement should relate to the contamination of components and not containers. The Commissioner agrees that the protection from contamination, as required in 211.84(c)(2), should relate to the contents of sampled containers. The final regulation is clarified in this regard.

235. Twenty-eight comments on 211.84(d)(1) stated in essence that the word "specific" should be deleted with reference to identity tests because there may not be specific identity tests for each component. The words "appropriate" and "if available" were suggested for use instead. The

Commissioner recognizes that the accuracy and precision of testing procedures vary. The purpose of 211.84(d)(1) is to assure that some identification procedure is used for each component and that it is as specific as possible.

Otherwise, the test has little value for purposes of identifying a material. This paragraph is reworded in recognition that specific identity tests do not exist for all materials.

236. One comment said interpretation problems could occur with the identity test requirement for active and inactive ingredients in 211.84(d)(1) in multiple-ingredient components. The suggestion was made that the wording be changed so that an identity test for each component had to be performed whether it was an active or inactive ingredient. The Commissioner is clarifying 211.84(d)(1) in the final regulation by requiring at least one test to verify the identity of each component of the drug product.

237. Five comments said there should be no requirement in 211.84(d)(1) for an identity test for inactive components. The Commissioner believes it is important to identify inactive components to avoid erroneously using unsuitable components to manufacture a drug product.

238. The use of organic chemical reactions as indications of product identity in bulk chemical processing was recommended by one respondent as an acceptable identity test under 211.84(d)(1). The Commissioner advises that the final regulation does not preclude organic chemical reactions as indicators of component identity, if appropriate.

239. A number of comments relating to validation of a supplier's test results recommended that that portion of 211.84(d)(2) be deleted. The argument was that the validation requirement would preclude the use of procedures other than those used by the supplier. One change in the wording was suggested: that the word "monitors" be used in place of

"establishes." The Commissioner believes that alternative procedures may be an acceptable means of validating methods used in the testing of materials by a supplier.

The regulations do not preclude the use of alternative methods. About the word "monitors" in place of "establishes," the Commissioner believes that the meaning of this sentence would be changed if the substitution were made. If a manufacturer wishes to rely on a supplier's report of analysis, the manufacturer must first establish that those reports are reliable. That reliability is established by the manufacturer's own testing which, when compared to the supplier's data, shows agreement within specified limits over a period of time. Once that reliability is established, then the level of the manufacturer's validation testing may be reduced and reliance on the supplier's report may increase. Continuing checks should be made on the supplier's reports because some kind of periodic monitoring must occur to assure the continued reliability of the supplier's test results.

240. One comment suggested that the word "complete" should be deleted from 211.84(d)(2) as a descriptive term for the supplier's report of an analysis. The Commissioner's intent in this paragraph is to allow for alternative routine testing where reliable reports of analysis are available for components. He finds that the criteria for accepting reports of analysis adequately provide for their proper application and that the modifying term "complete" is not necessary. The final regulation is revised accordingly.

241. One comment said suppliers' reports of analysis are not always reliable and suggested that several additional guarantees be required in 211.84(d)(2). They included, in addition to the report of analysis, a guarantee of the type described in section 303(c) of the act, a certification that the testing reported was done within 7 days of the report, and a guarantee that at the time of shipment/receipt that the component will still conform to protocol specifications.

Suppliers' reports of analysis must be validated to establish the reliability of the suppliers' analysis. Additional specified requirements relating to suppliers' test results do not now appear to be necessary for these regulations.

242. One comment expressed concern that the validation requirement in 211.84(d)(2) would lock a manufacturer into a single supplier, presumably because of the investment in validation procedures. The Commissioner advises that reliance on a supplier's report of analysis is not mandatory--it is optional in lieu of testing by the manufacturer. Although an investment in validation might persuade a manufacturer to remain with a single supplier, this does not constitute sufficient reason, in the Commissioner's opinion, to preclude the use of this approach by manufacturers. Competition among suppliers should not be adversely affected by this option. 243. One respondent proposed deleting the word "all" with reference to the phrase in 211.84(d)(2) that testing be done in accordance "with all appropriate specifications," apparently to allow for less stringent testing if deemed appropriate by the manufacturer. The Commissioner believes the suggested change would alter the meaning of 211.84(d)(2). The intent is that appropriate specifications be established. Once appropriate specifications have been set, it is not acceptable to test for less stringent specifications. 244. A comment suggested deletion from proposed 211.84(d)(3) (now 211.84(d)(4)) of the reference to microscopic examination, stating that it does not seem to relate to any of the other provisions in this section. The Commissioner recognizes that 211.84(d) could list various other types of examinations, but he does not believe it inappropriate to specify a particular requirement for microscopic examination when appropriate, while not listing others. For certain classes of drugs, particulate contamination is of increasing concern. Identification and classification of particulate matter may properly require microscopic examination. Therefore, the Commissioner believes reference

to microscopic examination is worthy of emphasis in the regulations. 245. Eleven comments on proposed 211.84(d) (4) and (5) (now 211.84(d)(5) and (6), respectively) indicated that requiring materials to be either approved or rejected after testing does not take into account other categories of material status into which materials could fall if they do not meet specifications. For example, comments said that materials could be reprocessed or approved for alternative uses and proposed that a revision be made to recognize these other possible classifications. The Commissioner agrees that destruction may not be the only way of disposing of materials which do not meet acceptance criteria. If materials are being tested for their acceptability for manufacturing a particular drug product and they do not meet those criteria, however, they must be rejected for that use. This requirement has been set forth in 211.84(e) now, rather than in (d)(5) and (d)(6). There is no prohibition against the use of such materials after appropriate reprocessing, or for other uses for which the acceptance criteria can be met. 246. One comment suggested that examination of material under proposed 211.84(d)(5) be limited to visible contamination. Other types of examination may be necessary to identify contamination, because contamination that is not visible may adulterate a material as significantly as visible matter. Therefore, the suggestion is rejected.

247. One comment suggested a new requirement be added to 211.84(d) that representative samples of materials be examined for filth or microbiological contamination. The Commissioner notes that other paragraphs in this section, particularly 211.84 (a) and (b), require testing of representative samples. There appears to be no need to repeat it in 211.84(d).

248. One comment said with regard to proposed 211.84(d)(5) that it is the manufacturer's responsibility to determine the need for testing for microbial contamination. The Commissioner agrees that it is the manufacturer's

responsibility to determine what materials are liable to microbial contamination, but having made that determination, the manufacturer must proceed to test those materials for such contamination.

249. The requirement in proposed 211.84(d)(5) for microbiological testing of materials liable to bacterial contamination was interpreted by one comment as requiring sterility tests for containers and closures used in aseptic filling operations. The Commissioner agrees that an evaluation of a final production of aseptically produced sterile products would include the testing of containers and closures. Once a procedure is validated, periodic testing and control monitoring are necessary to assure that the processing controls continue to work.

USE OF APPROVED COMPONENTS, DRUG PRODUCT CONTAINERS, AND CLOSURES

250. A substantial number of comments objected to the requirement that, without exception, approved components, containers, and closures must be used on a first-in, first-out basis. These comments pointed out, for example, that on occasion a manufacturer might wish to evaluate a new supplier, or equipment, or processes in relation to a new container; or that on occasion the oldest stock might be physically inaccessible for a short period of time.

Several comments deemed the regulation unnecessary because some containers are inert. The Commissioner believes that the concept of using the oldest approved stock of components, containers, and closures is fundamentally sound. Even inert containers may be subject to increased breakage, cracking, or other defects after prolonged storage. There may, however, be legitimate reasons for varying from this requirement in some instances. Therefore, this section is revised to provide for exceptions from the first-in, first-out requirement by adding a provision that deviation from this

requirement is permitted if such deviation is temporary and appropriate.

RETESTING OF APPROVED COMPONENTS, DRUG PRODUCT CONTAINERS, AND CLOSURES

251. Several comments on 211.87 did not agree that components, drug product containers, and closures should all be retested in accordance with established requirements. They maintained that components require specific retesting procedures to assure continued identification, strength, quality, and purity, whereas the likelihood of deviation of containers and closures from specifications because of deterioration is considerably less and should not require the same degree of retesting as components.

They contended that stating requirements for retesting components and containers within the same section by the use of qualifying statements like "appropriately" or "as necessary" would weaken the former to accommodate the latter. They therefore proposed that this section be divided into two subsections, one for retesting components and a second for containers and closures. The Commissioner believes that this section allows for different treatment of containers and closures versus components by use of the phrase "as necessary."

The Commissioner recognizes that all the objectives of retesting listed in this section--to reestablish identity, strength, quality and purity--are not necessarily applicable to all containers and closures because all containers and closures are not necessarily tested originally for all these attributes. He also recognizes that the period for appropriate retesting varies not only according to conditions of storage, but also according to the type of component and the type of container and closure. The Commissioner retains the wording of the proposal in the final regulation.

252. One comment suggested that the words "or examined" be added after the word "retested" in 211.87. The Commissioner agrees that examination is not precluded by this section if examination is the appropriate test for the attribute being considered. Therefore, this section is modified in accordance with the respondent's suggestion.

REJECTED COMPONENTS, DRUG PRODUCT CONTAINERS AND CLOSURES

253. One comment recommended that in 211.89 the words "lots of" be inserted between the words "rejected" and "components." The Commissioner rejects this recommendation since the requirement applies to all rejected components, drug product containers, and closures whether they be lots, batches, portions of lots or batches, or otherwise identified.

254. Several comments suggested that this section be expanded to deal with the subsequent disposition of rejected materials. The Commissioner notes that the criteria for reprocessing rejected materials are adequately covered in other sections of this part. It is not necessary to deal with other methods of disposition because they are varied, are within the manufacturer's discretion, and may include destruction, return to the supplier, or use in other products where specifications are met.

The Commissioner believes the major concerns of FDA are that rejected materials are not inadvertently used in a product for which they are not acceptable and that any such materials that are reprocessed and found suitable for reuse meet specifications, standards, and characteristics for the intended use.

DRUG PRODUCT CONTAINERS AND CLOSURES

255. A number of comments asked about the meaning of the word "container" in 211.94(a). For example,

respondents inquired about the applicability of the proposed requirements to shipping cartons and containers for holding of in-process materials. As recognized by the majority of comments received about this paragraph, the section heading introduces requirements regarding drug product containers and closures.

The Commissioner finds that minor editorial changes in the text will clarify that this section is intended to apply to drug product containers. Requirements elsewhere in the regulations deal with appropriate handling of components and in-process materials.

256. Several comments on 211.94(a) involved testing requirements for container and closure systems. One comment recommended that specific testing requirements be included in this section. Another comment said that once the suitability of a container-closure system had been established, it should not be necessary to test each lot in minute detail.

The Commissioner finds that specific detailed requirements for testing of the container-closure system are not necessary for this section. Usually, manufacturers already have the benefit of experience with containers fabricated from materials with well-known properties. Further, the requirement of 211.166, particularly paragraphs (a)(4) and (b), will provide substantial information relative to the suitability of a container-closure system.

Where the manufacturer does not have adequate information regarding the container-closure system, the responsibility is on such manufacturer to establish the suitability of the container-closure system for its drug product. The final CGMP regulations do not specify detailed testing of each and every lot of containers.

Manufacturers are responsible for the extent and manner of sampling and testing of drug product containers and closures.

Adequate sampling and testing of containers will depend on a number of factors. The duty of the manufacturer is to assure that the container-closure system meets appropriate specifications that have been established for a particular packaged drug product.

257. One comment suggested that 211.94(a) also specify that the container-closure system "be clean." Revisions in 211.94(c) clearly provide for the use of clean containers and closures.

258. All of the numerous comments on 211.94(b) requested that the requirement that container-closure systems "provide adequate protection" be modified to the limits of "normal" storage and use of the product or to limits of use and storage set forth on the label. The Commissioner agrees that the proposed regulation requires a level of protection that may not be possible to achieve in unforeseen circumstances. Therefore, the final regulations are revised to include the concept of foreseeable conditions.

The Commissioner believes, however, that the acceptability of container-closure systems under a relatively narrow range of conditions that might be considered "normal" is not sufficient. It is reasonable for manufacturers to consider conditions that can be expected to occur occasionally; for example, extreme temperature variations that may be encountered during winter and summer months for drug products that are in transit can be reasonably foreseen by manufacturers and should be taken into account when considering the suitability of container-closure systems.

259. About 50 comments were received concerning 211.94(c). Most suggested modification of the requirement that containers and closure systems always be cleaned before usage. Many indicated that although it was the drug manufacturer's responsibility to see that these items are clean,

manufacturers may not always have to perform a separate cleaning operation.

Examples of items which may not always need cleaning were cited, such as: caps, liners, blisters, neutralizers, and films. In proposing this requirement, the Commissioner intended that containers and closures be clean before use. In some instances this will require the manufacturer to perform separate and sometimes extensive, cleaning cycles.

In other instances it may not be necessary for the manufacturer to undertake a specific cleaning operation. In any event, containers should not be released by the quality control unit, as specified in 211.84(a), until procedures, standards, or specifications, established under 211.94(d) have been met. To clarify the intent of this section the word "cleaned" is changed to "clean."

260. The majority of the comments regarding 211.94(c) were directed at the requirement, currently in effect, that containers and closures be cleansed with water that has been filtered through a nonfiber-releasing filter of specified pore size. Comments strongly objected to this requirement for a number of reasons. A few read the paragraph as requiring that containers be recleansed with water, whether or not a cleaning cycle is necessary; several respondents noted that solvents other than water are used for cleansing; others objected to the pore size requirements because of high volume demands of cleaning cycles.

In addition, arguments were presented that by requiring filtration of cleaning water for injectable containers, new problems of microbial and pyrogen contamination are possible.

In particular, the United States Pharmacopeia submitted comments by the Subcommittee on Particulate and Chemical Contamination, National Coordinating Committee on Large Volume Parenterals (NCCLVP), whose committee membership

includes representatives from major health care organizations, industry, and government.

The NCCLVP expressed concern that the requirement for filtered cleaning water presents disadvantages and potential hazards that far outweigh the benefits. The specific reasons for their concern are as follows:

1. Water lines for transferring cleaning water for injectable containers are designed, constructed, and maintained to deliver large quantities of high quality water under high pressures. In order to maintain the integrity of these lines and the quality of the water, disruptions must be minimized. The need to routinely install, test, and replace bacteria-retentive filters of the type required will undoubtedly compromise the integrity designed into these lines.

Furthermore, the pressure drop resulting from the inclusion of such filters will jeopardize the quality of the wash.

2. Cleansing and rinsing procedures require copious volumes of water. Even with water containing low levels of microorganisms and particulates, significant accumulation of such contamination can occur on the filter surface. Proliferation of bacteria on the intact filter can lead to the generation of pyrogens or the growth of certain bacteria through the filter pores if a 0.45-micron filter is used. Since high flow rates and pressures are required, the chance for mechanical failure and breakage of the filter is increased, thereby increasing the risk for the passage of a bolus of bacteria.

3. Because of the microbial jeopardy described above, these filters will require scrupulous maintenance. Such efforts will result in significant penalties to the process in both material and labor costs.

It is the opinion of the Subcommittee on Particulate and Chemical Contaminants that if a fiber-releasing filter is not

employed in the process and a final rinse is performed with high-quality, microbiologically controlled water, it would appear to be unreasonable to introduce the disadvantages described above. The final regulation regarding asbestos particles in drugs for parenteral injection was published in the FEDERAL REGISTER of March 14, 1975 (40 FR 11865).

At that time the Commissioner had concluded that it was prudent to require that containers and closures for human injectable drugs be cleansed with water that has been filtered through a nonfiber-releasing filter of a specified pore size. In view of comments received, the Commissioner is concerned that the requirement for filtered cleaning water may introduce new problems that outweigh risks of potential asbestos particle contamination from the container cleaning operations.

The Commissioner notes that he raised a similar issue in the preamble to the CGMP regulations for large volume parenterals, published in the FEDERAL REGISTER of June 1, 1976 (41 FR 22202). Because of the comments received the Commissioner finds that there is substantial good reason to suspend, at least temporarily, the requirement that injectable containers and closures be cleansed with filtered water to remove fibers.

The Commissioner wishes, however, to serve notice that the issue of fiber removal from parenteral drugs, including where such fibers may be introduced through the cleaning cycle of containers, continues to be an important problem under review by FDA. Until FDA has additional information on the fiber content of cleaning water and the significance of such fibers, however, the final regulations are revised to delete the requirement for filtered cleansing water. But this action in no way affects the agency's position on fiber-releasing filters in the manufacture of injectable drug products for human use (see 211.72).

261. Almost all the comments on 211.94(e) said it was a restatement of the other parts of this section and therefore should be eliminated. One comment said the phrase "the holding of" was redundant since, by definition, containers are used "for the holding" of a product. The Commissioner finds that the requirement of the proposed paragraph is not necessary in this section because a similar requirement appears in 211.165(g). Therefore, he is deleting the proposed paragraph (e) from this section.

DOCUMENTATION OF CONTROLS

262. A number of comments suggested that 211.96 be deleted on the grounds that it duplicates provisions of 211.84. The Commissioner agrees that both sections deal with documentation of the receipt, testing, or examination and disposition of components, drug product containers, and closures. Therefore, 211.96 is deleted.

XII. PRODUCTION AND PROCESS CONTROLS

WRITTEN PROCEDURES; DEVIATIONS

263. One comment on 211.100 said written procedures for manufacturing and quality control should be reviewed and approved by "the appropriate organizational units" instead of by the quality control unit because the quality control unit does not necessarily possess an expertise greater than that in other units.

Another comment said the quality control unit does not have a sufficiently wide expertise to review and approve all areas of drug product manufacturing, including such areas as production, engineering, research, safety, and regulatory affairs.

A third comment said the requirement for approval of written procedures for manufacturing and quality control by appropriate organizational units other than the quality control unit should be deleted.

The Commissioner rejects these comments. He has not proposed that quality control have complete expertise in all of these areas. The requirement for review and approval of manufacturing and control procedures is clearly a requirement that the quality control unit review these procedures in light of what may affect the product in terms of safety and quality.

To remove from the quality control unit the responsibility for approving written procedures would diminish the authority and responsibility that should be vested in the quality control function. Further, based on the agency's experience with the industry, the Commissioner believes that the concept of quality control review and approval for procedures that have a bearing on the quality and safety of a drug product is current practice.

This section also properly requires review and approval by other appropriate organizational units. Therefore, the quality control unit's function does not replace the expertise that would be vested in other units.

264. Another comment on 211.100 said requiring review and approval by the quality control unit is infringing unreasonably on individual manufacturers in determining their own organizational structures.

The Commissioner does not believe that this requirement unduly dictates organizational structure. For example, it does not designate to whom the quality control unit or other organizational units must report.

265. One comment on 211.100(a) said appropriate units should be required to review, as well as draft and approve, manufacturing and control procedures. The Commissioner agrees and is inserting the word "reviewed."

266. One comment suggested that the word "justified" in the last sentence of 211.100(b) be replaced by the word "explained." Another comment proposed substitution of the word "approved." The Commissioner believes that the word "justified" properly reflects the intent. All production and process control procedures must be approved, whether initial or subsequent changes. It is not necessarily enough to "explain" or "approve" a deviation. There must be a valid reason for a deviation.

267. One comment on 211.100(b) said only significant deviations should be recorded and justified. Section 211.100(b) requires that written procedures shall include all requirements as specified in subpart F of the CGMP regulations. This subpart does not require written procedures for every conceivable or minute detail of production and control. When such procedures are essential, the Commissioner maintains that any deviation from them is

significant and should be recorded and justified. To modify the regulation as proposed would imply, however, that only some deviations are significant.

268. A comment proposed deleting from 211.100(b) the phrase "and shall be documented at the time of performance." Documentation of performance, in the Commissioner's opinion, certifies that the written procedures have been followed. He concludes that it is a necessary part of this section.

CHARGE-IN OF COMPONENTS

269. One comment on 211.101 stated that the heading "charge-in of components" is an unfamiliar phrase and is not defined. The Commissioner recognizes that not all firms use the same terminology to define similar phenomena. He believes the heading is clear when considered in light of the context of the section and that no change or definition is needed.

270. One comment said 211.101 is addressed to dosage form production and cannot profitably be applied to chemical manufacture. These CGMP regulations apply to finished dosage form drugs (under 210.3(b)(4) and 211.1) and are not binding requirements for chemical manufacturing. The Commissioner maintains that these regulations can serve as useful guidelines in the manufacture of chemicals. The agency plans to develop specific CGMP regulations on production of bulk drugs.

271. One comment said it would be difficult to follow the requirements of 211.101 when producing radiopharmaceuticals because the exact quantity of the radionuclide available before the production cycle begins is not known, and the components measurement must be performed aseptically. The Commissioner is rewording 211.101 to allow for its application to radiopharmaceuticals. Further, this comment will be

considered when specific CGMP regulations are proposed for radiopharmaceutical drug products.

272. One comment said the operation supervisor may or may not be the same person as the one checking the operation and suggested adding a new paragraph (e) to 211.101 to have the appropriate entries made on the batch record. The Commissioner believes that 211.188(b)(11) adequately cover this.

273. One comment said 211.101(a) is ambiguous because the word "intent" needs defining. The respondent pointed out that antibiotic products are certified under published monographs permitting 85 or 90 percent of labeled claim as a basis for certification. The Commissioner notes that this paragraph does not prohibit the release of batches of drug products if the percentage of active ingredients is within acceptable limits.

The Commissioner recognizes that acceptable limits are in most cases a few percentage points above and below 100 percent of labeled potency. What is prohibited is the purposeful formulation of a product to yield less than the label declaration.

274. Several comments expressed concern that every active ingredient amount would have to be recalculated to provide 100 percent and that a new master production record would have to be prepared for each new lot of active ingredient because every lot of active ingredient may not have the same potency value.

The Commissioner believes that use of the word "intent" should be emphasized. Drug products must be formulated to provide 100 percent of labeled potency based on the usual assay of active ingredients. Active ingredients that are slightly above or below the usual value, but are within appropriate established specifications, may be used without reformulation

provided that the resultant drug product will provide a percentage of active ingredient that is within acceptable limits. The criteria for acceptance of components should be such that proper use will result in an acceptable drug product.

275. One comment said it is extremely difficult to formulate a biological product to fulfill the requirement of 211.101(a) because the potency value is assigned after the manufacturing process has been completed.

The Commissioner again emphasized the use of the word "intent." The example given in the comment does not show that there is intent to formulate such products at less than 100 percent of labeled claims; rather, it virtually precludes such an intent by the nature of that process.

276. One comment wanted to substitute the words "the amount of active ingredient specified in the master production and control record of the drug product" for the words "100 percent of the labeled amount of active ingredient" since over-the-counter drugs are not required by law to note the quantities of active ingredients in the labeling.

The Commissioner agrees with the object of the comment, but believes the suggested wording is inadequate because it would not prohibit the master record from containing a formulation intended to provide less than 100 percent of labeled potency. Instead, the Commissioner is revising the final regulation by adding the phrase "or established" after the word "labeled." This would therefore include formulations established through new drug applications and over-the-counter drug monographs.

277. Many comments on 211.101(a) said that: (1) It appears that all components must be weighed or measured precisely; (2) clarification of this section is needed to allow for the use of bulk components without previous subdivision, weighing, or measuring; (3) clarification is needed to allow for direct weighing of components into a batch.

The Commissioner finds that 211.101(a) as written is not flexible enough to permit procedures such as are given as examples in the comments. Therefore, the first sentence of this paragraph is revised to read as follows in the final regulation: "Components for drug product manufacturing shall be weighed, measured, or subdivided, as appropriate."

278. Numerous comments requested clarification of 211.101(b) regarding the necessary identification of component containers. The comments pointed out that in some instances components are dispersed, but that the manufacturing department would make that decision for specific batch usage. Several comments said the identification information was available through alternate control systems. The Commissioner believes that, as written, the final regulation takes into consideration the physical dispersal of components. Comments that the required identification information is available through alternative control systems gave no examples; therefore, no change is made in the regulation.

279. Several comments objected to the word "strength" in 211.101(b)(4) and wanted it deleted. The Commissioner rejects these comments. If a component container does not adequately identify the batch in which the component is to be used, there is a potential for mixups. The term "strength" is defined in 210.3(b)(16), so there can be no ambiguity in its meaning.

280. Two comments suggested that use of component lot numbers and product lot numbers on the same container presents a possibility of mixup since the wrong numbers may be written on the batch record. The Commissioner finds that it is necessary to have this information for a complete drug product history. As a practical matter the requirement will probably not pose a problem because most firms already have number identification systems that readily distinguish

component lot numbers from drug product batch or lot numbers.

281. Several comments objected to the requirement in 211.101(c) that each container of component dispensed to manufacturing be examined by a second person. The Commissioner believes the requirement is necessary and does not believe it will be a burden to the industry. The Commissioner also notes that the substance of the requirement is no different from that stated in 211.40(a) of the CGMP regulations currently in force, and it reflects current industry practice.

282. Several comments said that in some cases, such as with bulk component systems, there are automated methods for checking that could replace a second manual check. The Commissioner wishes to point out that the use of automated systems is permitted under 211.68. The requirement of this section would be met if the second individual verifies that the automated system is working properly.

MANUFACTURING INSTRUCTIONS

283. Some comments suggested deleting 211.102 because the subject and intent are adequately covered by 211.100. The Commissioner agrees with these comments, and this section is deleted in the final regulation.

CALCULATION OF YIELD

284. Several comments on 211.103 said the requirement for determination of yields at each distinct phase of manufacturing, processing, packing, or holding is ambiguous and subject to varied interpretations in view of the agency's use of the terminology "each distinct phase." Others said some type of drug products do not lend themselves to a determination of yield at each distinct phase of manufacturing, such as certain biological products and those operations using

continuous runs. The Commissioner agrees because what is "distinct" is subject to different interpretation and not applicable in other cases. Therefore, he is revising the section to require yield determination at each "appropriate" phase of production.

285. Several comments said the requirement in 211.103 for independent verification by a second person is unnecessary. The Commissioner finds that independent verification is a current practice and has been, in substance, a CGMP requirement since 1963. Independent verification has been found to be a valid means of uncovering errors which might, if left undetected, adversely affect drug product quality. Therefore he rejects these comments.

286. Several comments said, in substance, that calculating the percentage of theoretical yield is not the only method of comparison. The Commissioner does not believe that the wording as proposed would preclude the use of, for example, a standard range of acceptable yield. Ultimately, however, acceptance must be based on a ratio of actual yield to theoretical yield.

EQUIPMENT IDENTIFICATION

287. Several comments on 211.105 pointed out that there are cases where several pieces of equipment are grouped together to perform a function and that in such situations, collective identification of the equipment should be sufficient rather than identification on individual components of the grouping. The Commissioner feels that such a procedure is acceptable only if the equipment is permanently installed and used only for one purpose and only one batch of a drug product can be processed on it at one time.

This procedure would eliminate the need to identify equipment when there could be no misunderstanding as to what drug product is being processed. In such cases of equipment

dedication, identification of the grouping can be considered as meeting the requirements of this section. The language of the final regulation more clearly provides for this situation.

288. One comment requested clarification of the terms "production" and "major equipment" as used in 211.105. The comment questioned whether equipment for label printing, insert folding, or other similar operations not used in dosage form preparation should be identified in the batch record. Operations such as label printing and insert folding are not generally performed as a function of the production of a particular batch of drug product. Such operations are not suitable for consideration under 211.105, but are subject to the requirements of 211.122.

The phrase "major equipment" is used in 211.105 to distinguish it from minor equipment such as spatulas, ladles, and scoops, for which a requirement for identification may be unreasonable. Because it would be impractical to categorize every known piece of drug manufacturing equipment, a determination as to what equipment should be identified must be based by the manufacturer on appropriate criteria.

289. A number of comments on 211.105(a) questioned the meaning of the term "processing lines" and requested a definition. The term "processing lines" is used in a broad sense to include the variety of equipment that may be used in a drug manufacturing plant. For example, it may include a liquid filling "line" or a packaging "line" or any other kind of "line" used to convey a product through an operation, or to and from an operation, such as a pipe used to carry liquid from a bulk tank to another part of the plant.

290. Several comments on 211.105(b) suggested that where a manufacturer has only one of a particular type of equipment, it is unnecessary to use a distinctive code or number to identify it in the batch records. It was recommended that the equipment could simply be named.

Since the intent of the code or number is to provide identification of the specific equipment used to process a drug product, the Commissioner has no objection to identifying the equipment by name under conditions specified in the comment.

Wording of this paragraph in the final regulation provides for identification of equipment, under certain circumstances, by name.

SAMPLING OF IN-PROCESS MATERIALS AND DRUG PRODUCTS

291. Many comments on 211.110(a) pointed out that all in-process tests identified in the proposal were not appropriate to all dosage forms. It was not the Commissioner's intent to require that the particular tests listed apply to all dosage forms. The tests identified were meant to be examples of the types of tests that should be run on various dosage forms, but were not necessarily appropriate to all. Therefore, to make his intent clear, this paragraph is revised to show that these controls shall include those listed, where appropriate.

292. Two comments on 211.110(a) indicated that the word "manufacturing" should be modified by the word "major" and that the word "variability" should be modified by the word "significant." The Commissioner is not changing the wording because minor manufacturing problems may cause major manufacturing defects.

293. One comment recommended that the first part of the opening sentence in 211.110(a) be deleted because procedures do not assure batch uniformity and integrity of drug products.

The Commissioner agrees that the written procedures do not in themselves assure drug product quality--the procedures must be administered to have an effect. The Commissioner notes, however, that the requirement includes that established procedures be followed. Therefore, the comment is rejected.

294. Several comments suggested deleting or revising the references in 211.110(b) to statistical methods for determining in-process specifications. Some comments said statistical procedures for this purpose were not well understood either by industry or by FDA. Others said other means of determining in-process specifications should be allowed in addition to statistical means.

One comment said manufacturers with tight limits and little batch variability would be penalized by this requirement. Another comment was that, because finished product specifications are arbitrarily derived, use of statistical techniques during in-process phases would be inappropriate. Several comments indicated that, in the case of new products or new manufacturers, there is no manufacturing history so other means of developing in-process specifications should be permitted.

The Commissioner is persuaded that there are other valid means of developing in-process specifications as alternatives to statistical methods. Therefore, the final regulation is revised to provide for application of statistical procedures, when appropriate.

The Commissioner emphasizes, however, that in-process specifications must be meaningful in terms of achieving the desired finished product characteristics. Further, after product histories are developed, the Commissioner encourages manufacturers to perform statistical analyses on their products and processes with a view to controlling batch-to-batch variability to the maximum extent possible.

295. Three comments suggested that 211.110(b) requires in-process testing, whether needed or not, but that paragraph (a) only requires testing in an optional sense. The Commissioner recognizes that there are instances where the effect of variability during drug manufacturing phases cannot be predicted in relation to the drug product. Further, there may be instances where there are no suitable points, during in-process phases, to sample and test. The final regulations are reworded to clarify this.

296. One comment suggested that allowance be made in 211.110(b) for the use of in-process tests for adjustment purposes. The Commissioner finds that specific references to in-process tests for adjustment purposes are unnecessary. The regulations provide flexibility to the manufacturer for establishing procedures for any appropriate in-process test and determining the significance of testing results.

297. As noted above in paragraph 199, the Commissioner concurred with recommendations to transfer requirements for in-process materials in proposed 211.88 and 211.89 from Subpart E to Subpart F in new 211.110(c) and (d). comments on the proposed sections will be addressed in this section of the preamble, using the new section numbers.

298. A number of comments suggested that 211.110(c) (proposed as 211.88) is overly restrictive because it would require complete testing of in-process materials at each significant step in production. It was suggested, too, that in-process testing done during production to determine the need for equipment adjustment or to monitor equipment adjustment need not be reviewed by the quality control unit. The Commissioner concludes that the intent of this section, as modified in the final regulation, is clear.

There is no requirement that the quality control unit approve or reject in-process materials at the completion of each and every individual test or examination. Approved written

procedures may provide for minor equipment adjustments, checking, and monitoring of in-process material production. However, at the completion of a significant phase, for example, the quality control unit must approve or reject the in-process material before proceeding to the next phase.

299. One comment suggested defining the terms "significant stages" and "long periods" in proposed 211.88 (now 211.110(c)). To maintain the flexibility necessary for these regulations, the Commissioner finds that it would not be practical to define either of these terms because they can cover many types of situations and products. They should be read within the context of the handling of specific products and the characteristics of those products.

A long period for holding an unstable product is obviously going to be quite different from a long period for holding a very stable product. In the same way, significant phases in the processing of drug products can vary greatly depending on the methods used and nature of the individual products. The determination of what is a "significant phase" and a "long period" must therefore be the responsibility of the drug processor.

TIME LIMITATIONS ON PRODUCTION

300. Several comments on 211.111 said there may be situations, such as mechanical failures or when material in bulk form has to be remixed, where the processing time would of necessity be extended beyond previously established limits. The Commissioner is revising this section to provide that deviation from established time limits may be acceptable if such deviation does not compromise the quality of the drug product. Such deviation must also be justified and documented.

301. One comment suggested that the words "when appropriate" be deleted from 211.111, placing the burden of

time limits on the manufacturer in all instances. The Commissioner rejects this suggestion in view of the general nature of these regulations. There may be instances where establishing time limits for production would serve no practical purpose in assuring drug product quality.

CONTROL OF MICROBIOLOGICAL CONTAMINATION

302. A respondent said that the requirements of 211.113(a) are redundant for "chemical processing" operations. The Commissioner is not sure what the comment meant by "chemical processing," but believes the comment may refer to in-process materials. If that is the case, the Commissioner does not agree.

The possibility of microbiological contamination is an important concern in drug products, both nonsterile and sterile, and requires emphasis in the regulations to assure that special precautions are taken, over and above other precautions to assure product acceptability, and to assure that no microbiological contamination occurs during processing which could have an adverse effect on the drug product.

303. One comment said 211.113 should not apply to medical gases because microbiological contamination is not a problem with such drugs. The Commissioner notes that there is little information available in the literature on microbiological and particulate contamination of compressed medical gases. If microbiological contamination is not a problem with such drug products, then appropriate procedures may be less extensive than those needed for more susceptible drug products.

304. Several comments requested clarification of the term "objectionable microorganisms" as used in 211.113(a) or suggested alternative descriptions of objectionable microorganisms such as harmful or pathogenic and fecal indicator microorganisms. The Commissioner deliberately chose the word "objectionable" as the appropriate modifier for

the term "microorganisms" in this paragraph to cover a number of circumstances.

Microorganisms could be objectionable by virtue of their total numbers or their detrimental effect on the product or by their potential for causing illness in the persons ingesting them. A definition of the term is not practical in the regulations, however, because the objectionable nature of a microorganism may develop only in relation to the unique circumstances of a particular formulation, a particular ingredient, a particular method of manufacture, or the conditions found at a particular firm. The Commissioner believes that the use of the word "objectionable" in a very broad sense is a more practical means of expressing the kind of control he intends.

305. One comment recommended that 211.113(b) be separated into two parts: Paragraph (b) would then apply to products manufactured by a sterile fill operation, and a new paragraph (c) would apply to a terminal sterilization process. The Commissioner believes this paragraph, as written, can apply to both sterile fill process and terminal sterilization process. In both instances there must be validation of the process used to show that it produces a sterile product.

306. One comment suggested that 211.113(b) would require the manufacture of nonsterile products under the same conditions required for sterile products. The comment further said that in some cases smaller numbers of microorganisms could be tolerated if kept under certain levels that could be established.

The Commissioner emphasizes that it is not his intent to require nonsterile products to be produced under sterile conditions. He has previously explained under paragraph 304, his intent in using the word "objectionable." Section 211.113(b) clearly states that it applies only to drug products purporting to be sterile.

REPROCESSING

307. Two comments suggested that the word "appropriate" be inserted before the phrase "established standards" in 211.115(a). The Commissioner finds that the suggested alternative wording offers no improvement over the proposed wording. Reprocessed batches must meet all established standards, specifications, and characteristics.

308. One comment suggested that the word "all" be deleted from 211.115(a) after the phrase "conform with." The Commissioner believes that the paragraph, as proposed, clearly states the intent regarding conformance with all established standards, specifications, and characteristics. Therefore, this suggestion is rejected.

309. One comment suggested alternative wording in order to clarify that 211.115(a) applies only to batches that are reprocessed. The Commissioner agrees with the substance of this comment and is adopting in part the alternative wording by revising the first three lines of 211.115(a). The Commissioner notes that the requirements for handling batches that are not reprocessed are adequately stated in other sections under Part 211.

310. A number of respondents objected to the direct authority given to the quality control unit under 211.115(b) in approving the reprocessing of nonconforming batches. They believe that such rejected batches should be either reviewed and approved subject to all normal tests by quality control or should be allowed to be reprocessed when the written procedures approved by quality control authorize and set forth the criteria for such reprocessing.

The Commissioner rejects these comments because they would not be consistent with accepted quality control practices. Reprocessing of drug products suggests that a problem occurred during production of a particular batch. The

Commissioner does not believe it is reasonable to expect that preexisting reprocessing procedures can be written to cover every reprocessing situation. Therefore, it is appropriate that individual reprocessing procedures be reviewed and approved by the quality control unit.

XII. PACKAGING AND LABELING CONTROL

311. Many comments suggested changing the title of this subpart to "Printed Packaging and Labeling Control." Some comments suggested inserting the word "printed" before "labeling and packaging materials." The Commissioner disagrees with the suggestions to change the title since this subpart includes controls for packaging materials that are not labeling. Insertion of the word "printed" to precede the word "labeling" would be confusing because, under section 201(m) of the act, labeling is written, printed or graphic material.

MATERIALS EXAMINATION AND USAGE CRITERIA

312. Several comments stated that the term "packaging materials" in 211.122 is too broad in that it would include such items as corrugated dividers, pads, and blister-packing liners. The Commissioner advises that the term "packaging materials" as used in this subpart refers to packaging materials other than containers and closures covered under Subpart E. Typically, unlabeled packing materials do not have to be examined as thoroughly as labeling materials. The Commissioner intends that 211.122, as written, allow for different treatment of unlabeled packaging materials and labeling materials.

313. There were several comments regarding 211.122, 211.186(b)(8) and 211.188(b)(8), stating that the word "labeling" is too broad because it could be construed as including advertising and promotional material and therefore is beyond the purview of the proposed CGMP regulations.

As previously discussed in paragraph 96, the regulations in this part set forth the facilities, methods, and controls to be used for the manufacture processing, packing, or holding of a drug product. Therefore, these regulations do not apply to labeling or advertising that is not associated with the drug product during its preparation under CGMP regulations.

314. One comment said 211.122 does not represent current practice, and no need for the proposed language has been demonstrated. The Commissioner notes that this section, as finalized, does not differ substantially from existing requirements. He believes this section represents current good manufacturing practice and is a significant aspect of any firm's quality control program. He also believes that drug product recalls initiated because of packaging and labeling errors indicate that the controls described in this section are needed.

315. One comment suggested that the last sentence in 211.122(a), pertaining to release of packaging and labeling materials after approval by the quality control unit, be replaced. The respondent believes that the use of unreleased lots of labeling and packaging materials should be permitted as long as approval is obtained before marketing.

As discussed earlier in this preamble, in paragraph 217 regarding use of unreleased components, drug product containers and closures, the Commissioner cannot accept this suggestion. It is not acceptable quality control practice to use unreleased materials in any phase of production. The Commissioner believes that use of released components, in-process materials, containers and closures, labeling, and packaging materials is generally regarded by manufacturers as necessary to quality control.

316. Several comments recommended deletion from 211.122(a) of the words "in detail," and one comment said that, as written, the paragraph would require documentation of all minute details. The Commissioner recognizes that different materials such as unlabeled packaging materials, as opposed to labeling, will require written procedures of different degrees of complexity regarding their receipt, identification, storage, handling, and examination and/or testing. Therefore, the Commissioner is revising the phrase "in detail" to "in sufficient detail."

317. One comment understood 211.122(a) to require the quality control unit to examine each container of material before acceptance. The comment recommended statistical sampling of materials instead. The Commissioner advises that the degree of sampling will depend on the material to be examined or tested. The intent of this paragraph is to require at least a representative sampling of all labeling and packaging materials. The final regulation is clarified in this regard.

318. One comment recommended deletion of the first sentence from 211.122(b), as it is redundant based on the requirements cited in 211.122(a). The Commissioner believes that 211.122(b) as proposed clearly spells out the basis for approval or rejection and clearly states that rejected materials shall not be used in operations for which they are unsuitable. Therefore, he does not believe paragraph (b) to be redundant.

319. Two comments said 211.122(b) is overly restrictive in that it requires labeling or packaging materials not meeting specifications to be rejected even though the rejection may not be based on a serious defect, and thus the material could be used. The Commissioner asserts that it is up to the firm to establish appropriate specifications. The specifications should be realistic so as to assure the safety and quality of the drug product, but they need not be so restrictive as to prevent the use of materials that could not affect the safety or quality of the drug product.

320. One comment interpreted 211.122(b) to tacitly allow use of a provisional release concept for materials that are found to be out of specifications for their original use but would be suitable for use in other operations. Therefore, the comment said this concept should be stated explicitly in the regulations.

The Commissioner does not believe that this paragraph implies the acceptability of any kind of provisional release. Materials rejected for one use must be completely tested and/or

examined to determine their suitability for any alternative use prior to such alternative use.

321. A comment said labeling and packaging materials approved for use should be rotated so that the oldest approved stock is used first. The Commissioner agrees that use of the oldest stock first is a desirable practice for most materials. The attributes of these types of materials that are related to age, however, do not normally have an effect on the drug product, as would be the case with components, containers, and closures.

Therefore, the Commissioner has decided that a mandatory requirement for using the oldest stock first is not necessary here. He has required, though, in 211.122(e) that obsolete labeling be destroyed.

322. A number of comments on 211.122(c) said this is not current industry practice, that costs outweigh benefits, and consequently the paragraph should be deleted. The Commissioner agrees that the proposed requirement for disposition, including dates and personnel involved, is unnecessary for packaging materials and believes that it was those proposed requirements that were for the most part being objected to. Further, 211.125 establishes the more specific control requirement for labeling.

Therefore, 211.122(c) is modified to require only that records be maintained for labeling and packaging material indicating receipt, examination, or testing, and whether accepted or rejected. Many firms already record this information. The burden on firms not recording such information should not be too great because a record of this information is currently required for components; therefore, the firms need only incorporate packaging and labeling materials into the system already employed for components.

323. Several comments on 211.122(d) wanted the exclusion of packaging materials other than labeling and a less restrictive wording than "separate compartments" for labeling. The Commissioner is convinced that it is not necessary in most instances to separate unlabeled packaging materials in the same manner as labels and other labeling. Therefore, 211.122(d) is revised in the final regulation to apply to labels and other labeling only.

The Commissioner is also replacing the phrase "separate compartments" with the word "separately" because it may not be feasible to place into compartments bulky packaging materials that are labeled and therefore considered labeling.

324. One comment requested deletion of the phrase "or quantity of contents" in 211.122(d). The Commissioner rejects this request since labeling with different quantity-of-contents statements is in fact different labeling.

325. Many comments suggested deletion of 211.122(e) as redundant. Other comments objected to the word "destroyed." The Commissioner considered the comments and is convinced that this paragraph should be revised to avoid repeating requirements of 211.122(a) and (b). The final regulation refers only to obsolete and outdated labels, labeling, and packaging materials. Obsolete and outdated labels, labeling, and packaging materials must be destroyed to eliminate mixups between currently used labels, for example, and obsolete labels. Such mixups can lead to serious mislabeling incidents.

326. Five comments on 211.122(f) contended that gang printing is not a good manufacturing practice and should be forbidden. Although the Commissioner wishes to discourage gang printing, he does recognize that, under stringent controls, gang printing can be safely used.

327. Two comments dealt with monitoring of the printing procedure in 211.122(g). One said it should be worded "* * * shall be set up by one person and be inspected by a second person at the beginning of the run to assure * * *" and the other suggested "* * * shall be monitored by the QC unit to assure * * *." The word "monitor" is being used here to describe an in-process production check on a piece of equipment to assure that it is working properly. In such a case, the "monitoring" can appropriately be done by someone on the production line. The Commissioner notes that 211.134(a) and (b) contains a requirement for further examination for proper labeling. The Commissioner sees no need to revise this requirement.

LABELING ISSUANCE

328. One comment assumed that in 211.125 the term "labeling" must apply only to items associated with the unit package. It further said there is nothing to be gained by accounting for any advertising that is included with OTC packages or shipping cartons simply because of the legal definition of labeling under the act. The Commissioner advises that if the printed material referred to by the respondent is advertising under the act, then the CGMP regulations do not apply. However, as has been discussed previously, where labeling associated with a drug product during its preparation under CGMP regulations is involved, then the regulations in this section apply.

329. One comment questioned the meaning of "strict control" in 211.125(a) and recommended that this paragraph be expanded to include certain specific features of strict control, such as requiring locked labeling transport containers. The Commissioner believes that it would be impractical to list specific features of strict control that would relate to all firms. Numerous comments were received that objected to specifying a "how to" approach instead of an "objective" approach. This is an instance of the regulations stating an objective that is

sought and leaving the method of attaining that objective to the reasonable discretion and ingenuity of the firm. The Commissioner, therefore, rejects this recommendation.

330. One comment recommended that the words "and/or batch" be inserted in 211.125(b) after the word "master" because the master record does not contain the information regarding the lot number or the expiration date to be placed on the label. The Commissioner notes that the intent of this paragraph is to ensure that the proper labeling is issued to the batch. He agrees that, as this comment points out, it is the batch record that usually contains the lot or control number and the expiration date and is therefore amending the paragraph to provide for this situation by including the words "or batch" after the word "master."

331. Some comments on 211.125(c) asserted that labeling reconciliation does not detect vendor mixups or errors. The Commissioner agrees with this statement and notes that labeling is required to be examined or tested for these deficiencies by 211.122 before being issued for use.

332. Several comments suggested substituting the word "significant" for "any" in 211.125(c) because the proposed wording would require an evaluation if there was a discrepancy of only one label. The Commissioner believes that these objections are suitably resolved by revising the wording to allow deviations within narrow preset limits.

333. Some comments on 211.125(c) said that in situations where there is unique labeling, unique labeling equipment, single-product packaging lines, and other adequate quality control procedures, labeling reconciliation is unnecessarily expensive and time consuming and does not preclude misbranding.

The Commissioner believes that label reconciliation is important because labeling mixups are one of the major

reasons for recalls. Regardless of the sophistication of the labeling system used, lack of labeling reconciliation would be a weak link in the total control of labels from their receipt to their use.

334. One comment on 211.125(c) argued that the institution of elaborate control procedures for a half-dozen individually typed labels is more an annoyance than a hardship.

It is difficult for the Commissioner to believe that the reconciliation requirement, when applied to six labels, is either an annoyance or a hardship.

335. One comment on 211.125(c) said there is little reason to reconcile shipping container labeling. The Commissioner does not agree with this statement. Misapplication of labeled cartons can cause a recipient to wonder which is correct--the carton label or the container label. Furthermore, the Commissioner believes that such reconciliation is not overly burdensome or costly and is a current practice in the industry.

336. Several comments on 211.125(d) suggested that recoding of excess labeling be permitted in lieu of destruction. The Commissioner rejects these suggestions. The possibility of error outweighs any benefit that would be derived from salvaging labeling with obsolete lot numbers. The agency's experience indicates that the majority of drug firms destroy excess labeling that bears lot or control numbers.

337. Some comments suggested adding wording to 211.125(d) to denote when destruction of labeling should take place. The Commissioner believes that excess labeling bearing lot or control numbers should be destroyed as soon as possible after labeling of the batch and before labeling of any subsequent batches. In view of the requirements in 211.130(d), however, the Commissioner does not consider it

necessary to set forth exactly when destruction must take place.

338. One comment on 211.125(e) argued that cut labels and labeling should not be returned to stock because of the inherent danger of mixup, but rather should be counted and destroyed. The Commissioner finds that this suggestion would be too restrictive for those manufacturers who use cut labels. He believes that with proper control, cut labels can be used without the occurrence of mixups.

339. Some comments suggested incorporating proposed 211.125(f) into 211.125(c) where much of the intent is already covered. The Commissioner agrees with these comments and has revised the final regulations accordingly.

340. Several comments suggested deletion of the words "in detail" from proposed 211.125(g) (now 211.125(f)) because they are superfluous and potentially misleading. One comment said a standard of reasonableness should be employed for the intended purpose. The Commissioner notes that the words "in detail" could be construed as requiring inclusion of minute detail. Therefore, the Commissioner is inserting the word "sufficient" before the word "detail."

341. One comment suggested deletion of proposed 211.125(g) (now 211.125(f)) because it is unnecessarily repetitive of 211.125(c). The Commissioner does not agree that this paragraph is redundant. Section 211.125(c) requires the employment of certain procedures, whereas paragraph (f) requires those procedures to be in writing and to be followed.

PACKAGING AND LABELING OPERATIONS

342. Comments on 211.130(a) suggested that mixups and contamination can be prevented by spatial separation as well as by physical separation as required in 211.130(a). In using the word "physical," the Commissioner intended that

spatial separation be considered as a type of physical separation. To preclude misinterpretation, he is revising this paragraph to clarify that spatial separation can be an acceptable method of separation.

343. One comment suggested insertion of the phrase "the probability of" between "of" and "mixups" in 211.130(a). The Commissioner rejects this suggestion because he believes it would make the paragraph confusing.

344. One comment suggested that the word "container" be inserted between the words "product" and "with" in 211.130(b). The Commissioner finds that it is not the purpose of CGMP regulations to specify all appropriate labeling, containers, or shipping cartons that should be required to bear a lot or control number. It is sufficient for these regulations to require that the manufacturing history of the drug product can be determined from a lot or control number.

345. One comment on 211.130(c) suggested that the word "batch" be replaced by the word "appropriate," because in large operations, records may be kept according to production runs, which may include a number of batches. The Commissioner rejects a substitution for the word "batch." it is the intent of the Commissioner that the batch production and control records be complete. Because the examination of labeling and packaging materials before use is a function of the production of a batch, the batch record would not be complete without this information.

346. One comment said certain packaging materials, such as corrugated paper, should not come under the requirements of 211.130(c). The nature and extent of the examination of packaging materials, including corrugated paper, will vary, but, nonetheless, an examination of some kind must be performed to assure that the material is suitable for its intended use. Packaging materials often provide product

protection, and the characteristics of packaging materials must be taken into account.

347. Some comments in 211.130(d) said it is not necessary to clear a line of packaging materials such as bottles, cotton, caps, circulars, or other general packaging materials if that packaging material is to be used on subsequent batches of the identical drug product to be packaged in the identical package unit.

Several comments regarding proposed 211.130(e) argued that packaging and labeling material common to the succeeding production run not be removed from the finishing area after the completion of operations and prior to the next run.

The Commissioner does not intend to require that packaging materials common to consecutive batches of a drug product be removed between such batches. Revision of 211.130(d) has clarified the requirements for removal of previously used packaging and labeling materials. Further, the Commissioner finds that the requirements of paragraph (e) are adequately covered in paragraph (d), and therefore proposed 211.130(e) is deleted in the final regulation.

DRUG PRODUCT INSPECTION

348. Several comments on 211.134 argued that the requirement for assuring that every container and package has the correct label would require 100 percent examination of the drug product during or after finishing operations. It is not the intent of the Commissioner to require 100-percent inspection of the drug product either during or after finishing operations.

To clarify this section the Commissioner is deleting the word "every" in 211.134(a). He is also replacing the word "assure" with the phrase "provide assurance." The Commissioner notes that this section as written in the final regulation requires a high level of confidence, but does not necessarily require 100-

percent inspection. The Commissioner encourages 100-percent inspection by either visual or automatic methods because drug product labeling mixups have been a major cause of recalls. Although 100-percent inspection might not provide absolute assurance, it would provide a higher level of confidence that every container and package in a lot has the correct label.

349. A comment said the parenthetical phrase "(visually, mechanically or electronically)" should be inserted after the word "examined" in line 2 of 211.134(a). The Commissioner notes that 211.68(a) permits the use of precision automatic, mechanical, or electronic equipment in all phases of drug product manufacture, processing, packing, and holding. Therefore, there is no reason to repeat this statement in each section where such equipment might be used.

350. A comment argued that the wording of 211.134(b) implies that the "representative sample" should be taken from sealed and palletized shipping cases. If shipping containers are labeled to contain a particular drug product, then it is the Commissioner's intention that individual shipping containers be examined to assure that the correct drug product is in the appropriate containers. A lot or batch does not necessarily have to be sampled after it has been palletized because, generally speaking, palletizing is not considered as part of the finishing operation referred to in 211.134(b).

351. One comment on 211.134(b) recommended that, in addition to visual examination, an identity test be required on the drug product if the firm packs physically similar drug products. The Commissioner does not agree with the suggestion that this paragraph contain provisions for identity testing if the firm packs drug products that are physically similar. Section 211.120(d) and (e) provides for the clearance of packaging and labeling areas before use. Section 211.165 provides for physically testing the drug product after packaging. The purpose of this paragraph is to provide assurance that the correct labeling has been applied.

352. One comment said the results of the examination need not be recorded on the batch production or control records if they are recorded elsewhere.

The Commissioner rejects this comment. It is important that the batch production and control records be complete regarding the history of the batch, including the results of examination of the drug product after packaging and labeling. It is not essential, however, that all information that belongs in the batch production or control record necessarily be on one piece of paper.

EXPIRATION DATING

353. Many commented on proposed 211.137, which would require expiration dating for all drug products. A number of comments agreed that expiration dating was appropriate for certain drug products, for example, those subject to fairly short-term deterioration, but objected strongly to requiring expiration dating for all drug products and concluded that a requirement for expiration dating of all drug products would not benefit the consumer.

A few comments objected specifically to expiration dating for over-the-counter drug products or drug products whose active ingredient is known to be extremely stable and that have, for all practical purposes, an unlimited shelf life. Examples given of such stable products include naturally occurring chemical compounds that are mined from the earth, refined, packaged, and sold for medical purposes. A number of comments from consumers were very strongly in favor of expiration dating for all drug products.

The Commissioner notes a trend toward voluntary dating of many perishable consumer products, particularly food and drug products. He believes that this trend has been generated in large part by consumers and consumer organizations who have

expressed great interest in expiration dating of such products and by manufacturers responding to this interest.

The pharmaceutical industry has been aware for a number of years that FDA believes it is in the public interest for manufacturers to provide information regarding the stability of its drug products. In the preamble to amendments to CGMP regulations published in the FEDERAL REGISTER January 15, 1971 (36 FR 601), the Commissioner announced his conclusion that the interests of consumers must be served by the establishment of valid expiration dates for drug products.

At the time, the Commissioner expanded basic requirements in the CGMP regulations for stability testing to allow time for manufacturers to accumulate data to support expiration dating. In the preamble to the February 13, 1976 proposal, the background regarding expiration dating was discussed at length.

The Commissioner pointed out that a number of drug manufacturers were already voluntarily providing expiration dates for their products; many products such as antibiotics, biologics, and drugs liable to deterioration were already required to bear expiration dates; and the latest editions of the United States Pharmacopeia (U.S.P.) and National Formulary (N.F.) require expiration dating for all products subject to compendial requirements.

The Commissioner does not believe that expiration dating of drug products places an undue burden on drug manufacturers. Those who have been complying with the 1971 CGMP requirement for stability testing will, for most drug products, already have data available on which to base a suitable expiration date.

When new products are being manufactured or when stability data are not otherwise available, the new CGMP regulations in

211.166 clearly provide for a tentative expiration date based on several factors, including accelerated studies.

Although no sound arguments were represented to the Commissioner that expiration dating of most drug products would not benefit the consumer, the Commissioner has tentatively concluded that it may not be advantageous to consumers, in consideration of cost vs. benefit, to require expiration dating for human OTC drug products if their labeling does not bear dosage limitations and they are stable for at least 3 years, as supported by appropriate stability data.

Therefore, the Commissioner has elected to delay implementation of the requirement for expiration dating for these products and is proposing elsewhere in this issue of the FEDERAL REGISTER to exempt these products from expiration dating. The Commissioner expects that types of products that would be affected by this exemption would include a number of medicated shampoos, topical lotions, creams and ointments, medicated toothpaste, and rubbing alcohol.

The Commissioner advises that until comments submitted in response to this proposal for exemption can be carefully evaluated and a decision made as to the suitability of such an exemption, the Food and Drug Administration will not enforce the expiration dating requirements of this section for the type of products that he is proposing to exempt. The Commissioner believes it is significant that the types of products he proposes to exempt from expiration dating are acceptable for frequent and often prolonged use without dosage limitation, and typically the contents of the retail package are used in a relatively short period of time.

The Commissioner also notes that few of these products currently bear expiration dating, and he is not yet persuaded in consideration of the comments that the costs involved in requiring expiration dating for these products can be justified on the basis of the information available to him at this time.

354. After reviewing the comments from individual consumers, the Commissioner believes that some private citizens misunderstood the applicability of expiration dating for all drug products and believed that the requirement for expiration dating will extend to drugs dispensed by a pharmacist on the written order or prescription of a physician. Section 503 of the act specifies the kind of information that must be supplied by the pharmacist to the consumer regarding the prescription drug.

While the Commissioner has found that a number of pharmacists voluntarily indicate an expiration date on the prescription drug container given to the patient, such transfer of information is not required by law and, until the subject regulations are in effect, such expiration information will not be available to pharmacists for all prescription drug products.

The Congress is now considering bills to amend the act to provide for expiration dating on all prescription drugs dispensed to consumers. The agency supports such legislative proposals.

355. Several comments opposed the inclusion of expiration dating in CGMP regulations on the ground that the misbranding section of the act, section 502 and, in particular paragraph (h) of that section, provides for expiration dating to the exclusion of the adulteration section, section 501, especially paragraph (a)(2)(B) relating to CGMP regulations. Further comment was that regulations issued under section 502(h) of the act are subject to the administrative provisions of section 701(e) of the act, which includes provisions for a public hearing if requested.

The Commissioner rejects these arguments. No paragraph of section 502 of the act expressly refers to expiration dating. Paragraph (h) of section 502 describes products liable to deterioration and the packaging and labeling that may be necessary to minimize such deterioration.

Although expiration dating might be considered implicit in this paragraph, the Commissioner does not find any basis for concluding that only labeling referred to in paragraph (h) of section 502 of the act can be required to carry dated labeling, or that the only statutory authority for FDA to enforce expiration dating is under this paragraph.

He notes, for example, that where expiration dating is required by an official compendium such as U.S.P. or N.F., FDA has authority to enforce this requirement under paragraph (g) of section 502. Section 502(a)(2)(B) of the act clearly provides to FDA broad authority to assure the quality, purity, identity, and strength of drug products at least through the time of dispensing to patients or sale to consumers.

The determination of stability of a drug product and the reporting of this information through an appropriate expiration date are an integral part of the assurance of drug quality.

356. A number of comments opposed expiration dating specifically for over-the-counter drug products. The arguments were primarily that: (1) Many OTC drugs are extremely stable and that expiration dating is of little value for products whose stability can be measured in terms of many years; and (2) that any required expiration dating for OTC drug products should coincide with final regulations developed under the current OTC drug review process. In the latter case, comments expressed concern that labeling changes required by expiration dating and probable labeling changes and formulation changes required at a later date under final OTC drug review regulations would be an unfair burden on manufacturers.

The Commissioner notes that he has already discussed in paragraph 353, the interim enforcement policy regarding human OTC drug products that are stable and marketed without dosage limitations. But he sees no valid reason for separating requirements for drug expiration dating for prescription drug products and most OTC drug products. The

Commissioner recognizes that firms should ordinarily be free to select any expiration date that falls within the documented stability period, and the regulations permit manufacturers to use any expiration date that is supported by appropriate stability data.

Even if a manufacturer knows that the active ingredient of its drug product is stable for 20 or 30 years, without expiration dating it is unlikely that the user of the drug product is going to know this information. The Commissioner believes that expiration dating will be more than marginally beneficial to consumers even for drugs that are unusually stable. First, it will reinforce pharmacist and consumer confidence in the product, and thus will avoid unnecessary disposal and replacement of old but not outdated drug products. Second, it will prevent confusion for drug dispensers and probably consumers that would naturally occur in a system where some, but not all, products carried expiration dating. The Commissioner sees no undue burden on manufacturers in requiring expiration dating of over-the-counter drug products prior to final OTC drug monographs.

The Commissioner notes that a wide variety of methods for expiration dating of drug products are available and that many of these methods do not require changes or reprinting of labels. If formulation changes are required as a result of a final OTC drug monograph, the regulations in 211.166 provide for development of tentative expiration dates. Since the expert OTC advisory review panels will not be considering the expiration dating of OTC drugs as a routine matter in their deliberations, the Commissioner sees no valid reason for further delaying expiration dating for most OTC drug products.

357. Comment was received from the American Homeopathic Medical Association, representing the views of various aspects of homeopathic medicine, including manufacturers of homeopathic drug products, specifically requesting an exemption from the proposed requirement of

expiration dating and related stability testing for their products.

The basis for the request is that homeopathic drugs characteristically contain such extremely small quantities of active ingredients that the finished product cannot be tested by usual analytical methods. Further, because of the theory behind homeopathic medicine, regard for determining the specific level of active ingredient and the normal measures of stability are inappropriate.

The Commissioner notes that homeopathic medicine and drugs used for homeotherapeutics are unique and differ substantially from other forms of pharmaceutical products. Previously, the Commissioner has exempted homeopathic drugs from the Over-the-Counter Drug Review (see the FEDERAL REGISTER of May 11, 1972 (37 FR 9464)).

Further, homeopathic drugs were excluded from review under the NAS/NRC Drug Efficacy Study Review (DESI) and distributors of homeopathic drugs have not been required to list such drugs under the Drug Listing provision of the act. (Manufacturers, however, are required to register as drug establishments.) Because of the unique nature of homeopathic drugs, the Commissioner has reconsidered the value of stability testing and expiration dating for this small class of drug products and concludes the need for expiration dating and complete stability testing, as proposed, are unnecessary in this group.

The imprecise nature of determining extremely low levels of active ingredients for each of a large number of attenuations (dilutions) that may be prepared for each drug substance, and the fact that factors such as potency, absorption, bioavailability and other measures of effectiveness do not appear to be applicable to homeopathic drugs, have convinced the Commissioner that requiring an expiration date for such

products would be a burdensome requirement that would not result in any added assurance of drug quality to the user.

Certain provisions of the proposed stability testing requirements, especially those relating to determining an expiration date, are also inappropriate. On the other hand, some stability information, such as the compatibility of ingredients based on testing or examination and marketing experience, is necessary for this class of drug products.

The final regulations are amended in 211.166 by modifying the stability testing requirements for homeopathic drugs.

358. Several comments expressed concern whether small labels of some drug products could accommodate an expiration date. Several other comments raised questions regarding the applicability of the expiration dating to their own specific small-sized products. In one instance, a manufacturer indicated that it would be required to purchase new equipment in order to apply the expiration date to the crimp of the tube for a medicated cream.

In another instance a manufacturer indicated that its products were individually packaged in a way that the units stay with an outer packaging until all the individual units are used; it inquired whether each individually wrapped unit was required to bear an expiration date. The problem of certain labels being too small to accommodate statements required by FDA has been raised many times in the past. A specific regulation has been issued to address this problem (see 21 CFR 201.100(b)(6)).

Currently, a substantial number of drug products are packaged in a wide variety of containers, with a substantial range of label sizes, yet these often are marked with an expiration date. For example, a number of drug products for use in hospitals are being packaged in "unit dosage" containers that bear all the required information as well as an expiration date.

The Commissioner believes that technology and the availability of different methods of placing the expiration date on the immediate container are now at a state where it is reasonable to expect that any drug product package can accommodate an expiration date.

There will still be individual situations where it will be necessary to determine whether a particular packaging constitutes a protective or convenience wrap and therefore is not required to bear full labeling, or constitutes the immediate container, and therefore should bear all required labeling including an expiration date. If a packager of drugs has any question regarding this matter, FDA will render an opinion upon request from the packager.

The request should be sent to Advisory Opinions Branch (HFD-35), Bureau of Drugs, Food and Drug Administration, 5600 Fishers Lane, Rockville, Md. 20857, and should include full information regarding the packaging as well as examples of the packaging materials and labeling.

359. One comment expressed concern that the presence of an expiration date on small containers may serve only to detract from the conspicuousness of other information, including warnings and dosage recommendations. The Commissioner rejects this argument. The practicality and advisability of requiring specific items of information on the immediate container must always be evaluated in light of whether it might compromise or obliterate the value of entire labeling of the immediate container.

The Commissioner finds that a uniformly short statement of an expiration date will not interfere with the conspicuousness of other required information. Further, the Commissioner finds that there is no practical alternative to convey expiration dating information other than to place it on the immediate container.

360. Several comments were received regarding the need for expiration dating of cylinders of compressed medical gases. One comment noted that expiration dating of these drug products would not benefit the patient. The value of imparting stability information to consumers or to those who dispense drug products has been discussed previously.

As stated earlier, the Commissioner cannot agree that expiration dating of most drug products would not benefit the user, whether or not the patient is personally aware of the expiration date. The Commissioner sees no justification at this time for exempting compressed medical gases from the requirement of expiration dating.

361. One comment objected to expiration dating of OTC drug products such as absorbent cotton, gauze bandages, eye pads, triangular bandages, cotton balls, and surgical gauze. The comment was that these products last indefinitely and that some of these products, dating back from World War I, are being sold and are perfectly satisfactory.

Another comment expressed an opinion that, with regard to expiration dating, all attention seems to be focused on the stability of the drug formulation. The comment concluded that other factors, such as packaging and storage conditions, must contribute to the determination of an appropriate expiration date.

The Commissioner notes that these comments, apparently from opposite points of view, illustrate his concern that all persons should understand that there are other factors to be considered besides the stability of a specific active ingredient in determining a suitable expiration date; these include the stability of the inactive ingredients, the interaction of active and inactive ingredients, the manufacturing process, the dosage form, the container closure system, the conditions under which the drug product is shipped, stored, and handled

by wholesalers and retailers, and the length of time between initial manufacture and final use.

For example, the period of time in which the sterility of a drug product can be assured may be substantially less than the inherent stability of the active ingredient. Thus, the expiration date for a sterile drug product may have a different basis than that for a nonsterile drug product of the same active ingredient.

Container closure systems or tablet coatings, for example, may increase or decrease the shelf life of the drug product. Therefore, as mentioned earlier, a number of factors must be taken into account in considering a drug product's stability.

The Commissioner also notes that articles such as cotton, gauze, bandages, and eye pads are now considered devices and will be handled under the Medical Device Amendments of 1976 and are no longer subject to these CGMP regulations. Expiration dating for certain kinds of medical devices is now under consideration by FDA.

362. Several comments recommended that FDA consider requiring that expiration dates fall within the same 1 or 2 months of every calendar year. For example, it was suggested that all drug products bear an expiration date that would end in January (or January and July) of the calendar year for which the manufacture has established a date of expiration.

The comments indicated that such a procedure would not interfere with establishing dating periods in multiples of 6 months or 1 year and would allow persons who need to make inventories of drug product stocks to easily survey such stocks for outdated drug products. While the Commissioner sees merit in a provision that would allow all outdated products to be readily identified and removed only once or twice annually,

he believes that such a requirement would not be justified at this time.

Manufacturers may use an expiration dating scheme that will provide an appropriate uniform expiration cutoff date to facilitate inventory control over outdated drug products in the channels of distribution. The Commissioner will further consider utility and currency of such a practice and whether future regulations would be appropriate.

363. Several comments spoke to the issue of a maximum expiration date, such as 5 years, about which the Commissioner had requested information and data that would establish whether any fixed maximum arbitrary date is in the best interest of the consumer. Most comments expressed strong opposition to a fixed maximum expiration date.

One such comment expressed the view that a maximum expiration dating period would discourage development of improved stability formulations and packaging. Another comment, which supposed that a 5-year dating period is generally acceptable to the pharmaceutical industry, recommended that such maximum expiration dating period be adopted with provisions that the time period could be extended on the basis of adequate data.

This same comment suggested that an advantage of a maximum expiration date would be to limit the length of time the drug product is not under the control of the manufacturer. The time limit would reduce the possibility of damage by environmental agents, adverse changes in packaging materials, and obsolete labeling.

The Commissioner advises that his request, appearing in the preamble to the February 13, 1976, proposal, for information and data showing that the establishment of an arbitrary date (5 years or any other time period) is in the interest of the consumer, resulted in generally unfavorable comments and no

information or data to support public interest in a maximum expiration date, either by consumers or industry.

Therefore, the Commissioner concludes that he has insufficient information at this time to find that setting a specific maximum expiration dating period is suitable or desirable for drug products.

364. A number of comments objected to the word "statistically" or the phrase "statistically validated" used in 211.137(a) in reference to the use of a "statistically validated expiration date determined by appropriate stability test." The arguments were that for some drug products the expiration period is established based on characteristics or attributes (e.g., color of tablets) which are subjective and not amenable to statistical analysis.

For new drug products, stability data may be quite limited and there are insufficient data for meaningful statistical analysis. In such cases, a manufacturer stated, expiration dates are conservatively assigned. Another comment indicated that statistical validation is duplicative and open to dispute in interpretation. Several comments indicated that they were unsure as to what was required for statistical validation.

Another comment explained that expiration dates are currently derived from actual stability tests involving the use of accelerated stability tests. The comments said that such accelerated stability tests do not need to be statistically validated as long as there is adequate justification for use of the conversion factors that relate the conditions of the study to labeled conditions.

Another comment said the use of statistics to derive an expiration date is only one of many ways that a valid expiration date can be obtained. Most comments on this paragraph suggested deletion of the word "statistically" or the phrase "statistically validated." Several comments suggested

revised wording to incorporate the phrases "appropriate expiration date" or "statistically or mathematically validated date."

The Commissioner finds that 211.166 on stability testing, which has been modified in the final regulations, contains the requirements that are the basis for establishing an expiration date. An appropriate expiration date, determined in conformance with the provision of 211.166, will meet the requirements of 211.137; therefore, the statistical validation requirement is not necessary to 211.137. The final regulation has been revised to clarify this issue.

365. Several comments suggested that the 6-month delayed effective date proposed by the Commissioner was insufficient to allow accumulation of the necessary data to determine appropriate expiration dates. Several firms suggested a 3-year delayed effective date for this requirement; another suggested a 2-year delayed effective date. Another firm indicated that it was common industry practice to allow a 3- to 5-percent seasonal return and redistribution of OTC products.

This firm requested provisions in the regulations to allow for such redistribution from inventory of drug products that do not bear expiration dates. The Commissioner believes that the industry has been on notice concerning expiration dating for a number of years and should have data developed under the basic stability requirements that have been in effect since 1963. Because of such general widespread knowledge and the "state of the art" regarding expiration dating, a 6-month delayed effective date in adopting this requirement should be an adequate transitional period in which to establish expiration dating procedures.

To allow distribution (or redistribution) of labeled stocks, however, the expiration dating required by these regulations

shall not apply to stocks of drug products that have been labeled prior to the effective date of these regulations.

366. One comment said 211.137(a) and 211.166 are inconsistent in that 211.166 permits the use of tentative expiration dates based on accelerated studies combined with basic stability information.

In revising 211.137 in response to other comments, the Commissioner has included a specific reference in 211.137(a) to 211.166. As codified, 211.137 clearly refers to the use of appropriate stability tests and stability studies described in 211.166. Thus, the Commissioner now sees no possible contradiction in these two sections.

367. Several comments objected to the introductory phrase "to assure" in 211.137(a). The comments were that the phrase is an impossible restraint and that an expiration date cannot "assure" that a drug meets identity, strength, quality, and purity standards. The Commissioner cannot agree with these comments. In common usage, the word "assure" implies a confidence that can reasonably be expected. The purpose of expiration dating is to inform users of the drug product that they can reliably expect that the product meets the professed standards of identity, strength, quality, and purity at the time of actual use.

368. One comment suggested that 211.137(a) should provide that adherence to dating periods in approved new drug applications (NDA's) would constitute compliance with this section. The Commissioner believes that it is unnecessary for the regulations to specify that adherence to dating periods in approved NDA's would constitute compliance with 211.137(a). Dating periods for products covered by approved NDA's are based on stability data submitted as part of the NDA's. These stability data have generally come from testing programs that fulfill the requirements of 211.166. If so, then such data also

fulfill the requirements of 211.137(a). If not, the NDA probably was approved many years ago and new testing, using more sophisticated techniques, is appropriate. For such products, the new CGMP requirements should not be and are not met by the approved NDA, and testing complying with 211.166 is required.

369. Several comments recommended that 211.137(a) be revised to include a statement to the effect that a drug product would not be required to bear an expiration date if it is determined on the basis of appropriate stability tests and on distribution and consumer usage patterns that the product will be consumed before significant deterioration occurs.

The Commissioner notes that he has considered stability and consumer usage patterns in establishing the interim enforcement policy discussed in paragraph 353 of this preamble. But he does not agree that the suggested revision would be suitable for all drug products, namely, prescription drug products and OTC drug products with dosage limitations.

Such provision would ignore a basic principle of expiration dating--that the manufacturer furnish information to reduce the chances of outdated drug products being consumed. The Commissioner does not think it is realistic to assume that every unit of a drug product will be consumed within a specific period of time, notwithstanding the considerable experience many manufacturers have regarding distribution and consumer use patterns.

Information regarding distribution and consumer use patterns, however, will serve to assist manufacturers to estimate the quantity and duration of stability information that would be worth developing; that is, if a supplier is confident that more than 90 percent of a product is out of the distribution chain in 3 years, the supplier may not wish to incur the expense of establishing a 5-year stability for the product and labeling it with a 5-year expiration date.

370. Some comments said proposed 211.137(b) was somewhat redundant when viewed in light of paragraphs (a), (c), and (e) of this section. The comments also recommended that if paragraph (b) were retained, the references to appropriate statistical analysis should be deleted. One comment recommended that paragraph (b) be revised to include mathematical use as well as statistical analysis. Another comment stated that the phrase "readily available data" should be further defined.

The Commissioner finds that with minor editorial differences the essential provisions of this paragraph also appear elsewhere in 211.137. Therefore, he has decided that the proposed 211.137(b) will be deleted.

371. A number of comments objected to the provisions of proposed 211.137(c) (recodified as 211.137(b) in the final regulation), specifically suggesting that drug products suitable for storage at room temperature not be required to bear appropriate storage conditions on the labeling. The intent of proposed 211.137(c) is to relate expiration dates to any storage conditions determined by the manufacturer of a drug product to be important and thus stated in the labeling.

A manufacturer may conclude that the expected normal handling conditions of the drug product do not require specific labeling instructions, or the manufacturer may elect to include any special handling or storage instructions to preserve the product's stability. An editorial change in the final regulation clarifies that storage instructions are not required in every instance.

372. One comment suggested that when proposed 211.137 (d) and (e) are read in conjunction with 201.17, it is obvious that expiration dates are required only for labeling described in 201.17 and therefore package inserts are excluded. The comments suggested that the language in the

section be revised to specifically exclude package inserts from a requirement to bear expiration dates.

The Commissioner sees no reason that the regulations exclude, by name, package inserts from a requirement to bear an expiration date. The regulations in 201.17 and, by reference, in 211.137, clearly specify which labeling is required to bear expiration information. To designate, by name, the labeling not required to bear such information is impractical because it includes more than the package insert and it is unnecessary and potentially confusing.

373. One comment recommended adding a new paragraph in 211.137, which would provide that in the case of licensed biological drug products, an expiration date, if applicable, either shall be determined by regulations specific for the product involved, or shall constitute part of the product license. The Commissioner cannot adopt this suggestion. A biological drug product should bear an expiration date even if one has not been specifically established for that product either in regulations for the drug product involved or as part of the product license.

XIII. HOLDING AND DISTRIBUTION

WAREHOUSING PROCEDURES

374. A comment said 211.142 should not require rigid physical separation of quarantined drug products before release by the quality control unit.

The Commissioner did not intend, nor does this section state, that rigid physical separation of quarantined drug products is necessarily required before release by the quality control unit. The degree of separation necessary would be dependent on other steps taken to assure that quarantined drug products are not used prematurely. For example, proper paper control or computer systems could offset the need for physical separation.

375. One comment recommended that the words "of temperature, humidity, and light" be deleted from proposed 211.142(b) because humidity and light are not controllable in a normally operated warehouse. The Commissioner disagrees that humidity and light cannot be controlled in a warehouse. However, he notes the regulation does not require these factors to be controlled unless the identity, strength, quality, and purity of the drug products would be affected.

The Commissioner believes that the regulation as written clearly requires that all drug products be stored under conditions that are consistent with maintaining the stability of the product. The conditions of storage will vary according to the particular product; hence the use of the word "appropriate" in this paragraph.

At the very least, storage conditions should always be such that there are no extremes. If the conditions of temperature, humidity, and light are extreme enough, almost any drug product would be affected.

DISTRIBUTION PROCEDURES

376. A comment on 211.150(b) said a requirement of lot number traceability is inappropriate and unnecessary when applied to the great majority of drug products for which the incidence of recall is extremely low. The Commissioner notes that this requirement is already in the existing CGMP regulations and is "current practice." He does not have information to support a contention that certain drugs are less likely than others to be recalled. Therefore, the Commissioner cannot accept this comment.

377. One comment said 211.150(b) should be deleted and 211.150(a) recodified into the introductory text of 211.150 because the act does not provide for recalls and because the objective of 211.150(b) is substantially covered under 211.196. The Commissioner does not believe that these two sections are redundant. Section 211.196 requires that distribution records be kept containing certain information.

Section 211.150(b) requires that distribution recordkeeping systems include the capability of identifying the distribution of any specific lot so that a recall may be facilitated. The Commissioner also does not believe that 211.150 mandates recalls. Section 211.150 recognizes that it is a current good manufacturing practice within the pharmaceutical industry to have appropriate systems to carry out the occasional recalls or withdrawals from distribution of drug products.

These actions are generally voluntarily undertaken by manufacturers. Because such mechanisms are a current and good practice, the Commissioner has legal authority under section 501(a)(2)(B) of the act to require them for all drug suppliers. The question of FDA-requested recalls is subject to separate regulations published in the FEDERAL REGISTER of June 16, 1978 (43 FR 26202).

378. One comment said the distribution records maintained by compressed medical gas suppliers are adequate to accomplish 211.150(b), but the requirement of 211.196 calling for the lot number on distribution records is unnecessary. Further comment said compressed medical gas lots are distributed in a very small geographical area and to a very limited number of accounts, and recall is a much simpler problem for medical gases than for the widely distributed multiple-unit lot drugs.

The Commissioner fails to understand how the intent of 211.150(b) can be accomplished without meeting the requirements of 211.196, and no such information was provided in the comment. The intent of 211.150(b) is that a firm be able to determine how much of a given lot, if any, was shipped to each consignee and on what date.

The Commissioner does not believe that compressed medical gases should be exempt from this requirement, because they are potent drugs, and distribution accountability is of as much importance in case of recall of them as for any other drug.

379. One comment said the phrase "and appropriate" should be inserted after the word "possible" at the end of the proposed 211.150(a).

The Commissioner agrees with this comment. In addition, the wording in the final regulation for this section has been revised to make it consistent with 211.86 as it pertains to the first-in, first-out concept. The final regulation provides that deviation from the first-in, first-out requirement is permitted if such deviation is temporary and appropriate.

XIV. LABORATORY CONTROLS

GENERAL REQUIREMENTS

380. One comment recommended that the word "justified" in the last sentence of proposed 211.160(a) be changed to "explained." It is not enough, in the Commissioner's view, that a deviation from standards be explained. The deviation must be supported by sufficient reason to show that it is needed and has no adverse impact on the drug product. Therefore, the recommendation is not adopted.

381. A comment requested a definition for "specification" in 211.160(a) so that it would describe a general category rather than a single document, and specifications could be prepared as separate documents for separate areas.

The Commissioner does not believe that, as written, the regulation requires that all specifications for all areas, such as sampling and testing, be a part of the same document. The word is used here in a general sense rather than as a reference to a single document.

382. One comment said 211.160(a) is ambiguous because it does not define requirements. The comment asked whether documentation is needed showing completion of requirements. The Commissioner advises that 211.160(a) is intended to refer to requirements that appear throughout Subpart I--Laboratory Controls.

A wording change in the final regulation clarifies this intent. With regard to the respondent's question concerning documentation, the Commissioner also advises that 211.194(a) contains a requirement for documentation.

383. Two comments proposed deleting the references in 211.160(b) to sampling plans and testing procedures and merely requiring documentation of what was done. The reasons for proposing this deletion were not made clear. The Commissioner believes that adequate controls include not only standards and specifications but also the sampling plans and testing procedures to determine acceptability.

These plans and procedures must be determined in advance of implementation--otherwise no systematic or comprehensive evaluation of the acceptability of materials and finished products can be assured.

384. A comment suggested inserting the phrase "or a reference to" after the word "description" in the sentence referring to descriptions of sampling plans and testing procedures in specifications. The Commissioner interprets the comment's concern to relate to the extent of the description required for the sampling and testing procedures used when these are set forth in detail in other documents.

The description depends on a number of factors, but certainly could include references to authoritative procedures such as the official compendia. The Commissioner does not believe the language need be modified, however, because he believes the word "description" provides sufficient latitude for the use of references, where appropriate.

385. A comment said the requirement in 211.160(b)(4), providing for remedial action in the event equipment calibration checks showed problems, is impractical because a course of action for each possible event could not be written. Instead, it suggested the paragraph read "* * * provisions for investigations to determine the necessary action."

The Commissioner believes that broad instructions can be developed for remedial action. The regulations in this section do not specify the detail in which such provisions must be

developed. In some cases, these instructions could provide principally for an investigation to determine the cause of a problem. In other instances, for example, where a problem can be expected to occur regularly, detailed instructions may be practical.

386. Several comments felt that inclusion in 211.160(b) of components, drug products, and in-process materials with containers, closures, and labeling was irrational. Controls throughout this section are only required as appropriate. It is not the Commissioner's intent to require inappropriate standards and testing. The substance, extent, and complexity of controls will vary with components, container, closures, and labeling, but suitable specifications, standards, sampling plans, and test procedures are necessary for each.

TESTING AND RELEASE FOR DISTRIBUTION

387. Comments on 211.165(a) pointed out that potency assays are often tests for identity, and therefore the reference to identity tests should be removed. The Commissioner does not believe that every potency assay would also serve as an identity test. In those cases where one test can suffice for both purposes, the wording of this paragraph would accept a single test.

388. One comment asked for an exemption from the prerelease sterility and pyrogen testing requirements of 211.165(a) of shortlived radioactive materials. The Commissioner recognizes that for short-lived radiopharmaceuticals it is not possible to obtain results of these tests before the active material degrades below a useful level.

Therefore, the final regulations in 211.165(a) permit release of those specific batches that are undergoing sterility and/or pyrogen testing, prior to completion of those tests, provided such testing is completed as soon as possible.

389. Several comments requested clarification of 211.165(a) to determine whether it means that potency assays have to be done at both the bulk and packaged drug product phases, or only at the bulk phase. The Commissioner purposely worded this paragraph so that manufacturers could choose to do potency assays at either phase, but certainly before release for marketing.

There is no intent, once the product is in its finished dosage form, to require potency testing of more than one phase by the manufacturer. The Commissioner believes the paragraph is clear in this regard. 390. Two comments maintained that identification and potency testing of each active ingredient in a combination product or in small batches of OTC products constitutes a highly inflationary procedure.

The Commissioner believes that testing to assure that a product is what it purports to be is basic to a quality control program for any drug product. Further, he notes that the substance of this requirement has been in the CGMP regulations since 1963 and is generally a current industry practice. Therefore, he finds that such a basic procedure should not have a significant inflationary impact or that this cost is unjustified in view of the assurances the procedure gives the consumer. The comments are rejected.

391. A comment suggested limiting 211.165(c) to sampling by deleting references to testing, on the grounds that 211.160 adequately covers the requirements for written testing plans. The Commissioner notes that 211.160 has general objectives regarding sampling and testing of drug products. Requirements for release of drug products are more specifically described in 211.165. Therefore, the Commissioner declines to accept this comment.

392. Several comments objected to or redefined the concepts of acceptable quality level (AQL) and unacceptable quality level (UQL) used in establishing acceptance criteria and

statistical quality control criteria as proposed in 211.165(d). The comments pointed out that the concepts of AQL and UQL are not uniformly interpreted, and their use in establishing acceptance criteria and statistical quality control criteria is not uniformly applied.

Comments expressed concern that the concepts of AQL and UQL as acceptance criteria are premature and not currently a part of good manufacturing practice. One comment suggested that these proposed CGMP regulations would require extensive changes in testing procedures, facilities, and use of manpower. Several objections were raised relative to the "usually 95 percent" level of high probability of acceptance.

Respondents pointed out that this figure might be applicable for some pharmaceutical dosage forms, but would be too high for others. As anticipated by the Commissioner, the concepts of AQL and UQL in establishing acceptance and statistical quality proved quite controversial.

From an analysis of the comments, the Commissioner believes that it is impractical at this time to establish a uniform system of AQL and UQL as proposed in the regulations. Section 211.165 is therefore modified to allow greater latitude in establishing acceptance criteria, while retaining the basic requirements that acceptance criteria for sampling and testing, and for acceptance levels, be based on appropriate statistical quality control criteria.

The Commissioner is convinced that sound statistical methodology should be applied to the procedures for testing of attributes or variables that impact on the quality of drug products and the evaluation of the results of such testing to determine acceptance or rejection of the lot. The uses of AQL and UQL are examples of statistically derived levels for acceptance or rejection. The Commissioner believes that more study must be given to this aspect of manufacturing practice

and advises that in the future FDA will invite additional industry comment regarding revision of this section.

393. Several comments asked, with regard to 211.165(e), whether official compendia test methods or methods from recognized sources have to be validated. The comments also recommended that guidelines be provided for documentation. It is not the Commissioner's intent to require the validation of authoritative test methodology. Section 211.194(a)(2) of these regulations indicates that reference to official sources will suffice as documentation of a validated method.

The intent of this section is that assurance of accuracy and reliability be provided for all test methods used. In the case of methods from official sources, such as compendia, reference to the source is documentation enough. For methods modified or developed by the firm or some other unofficial source, validation of the method must be provided. To clarify this issue, the final regulation in 211.165(e) refers to 211.194(a)(2).

394. A number of comments on 211.165(f) proposed that laboratory reference standards received from official sources and/or with a protocol need not be tested. In addition, respondents recommended that secondary in-house standards should be tested against reference standards. Insertion of "standard solutions" was also suggested in this section.

One respondent suggested inclusion of a requirement for an expiration date on standards. In considering the comments in light of requirements elsewhere in the regulations, particularly 211.160(b), the Commissioner concludes that the proposed requirements in 211.165(f) should not be adopted as proposed.

The Commissioner recognizes that laboratory reference standards can be interpreted to mean either standard

reference materials prepared by a firm's own laboratories, or standards received from outside sources, e.g., official U.S.P. reference standards or FDA reference standards. Further, the Commissioner recognizes that complete testing by the user of many reference standards is not practicable although, generally, a specific identity test should be performed to verify such standard. The Commissioner finds that the requirements in 211.160 provide the manufacturer the necessary flexibility to establish appropriate laboratory controls over the receipt or preparation of reference standards and to verify that such reference materials are suitable for their intended use.

Therefore, proposed 211.165(f) is deleted in the final regulation.

395. Several comments objected to the use of the word "statistical" in proposed 211.165(g) (redesignated 211.165(f) in the final regulations), stating that statistical criteria are not always relevant. The Commissioner is deleting the word "statistical" in the final regulation because the phrase "and any other relevant quality control criteria" is sufficient to include statistical criteria where appropriate.

396. One comment requested deletion of the entire proposed paragraph (g) of 211.165, because it is repetitive of 211.84(e). The Commissioner agrees that there is repetition between 211.84(e) and proposed 211.165(g) (now 211.165(f)); however, he notes that the former does not cover drug products that are covered under the latter. The final regulation is revised to eliminate repetitious requirements.

397. Several comments objected to the wording of the second sentence of proposed 211.165(g). They contended it is not possible to determine beforehand whether reprocessed material will meet appropriate standards and specifications.

The Commissioner accepts these suggestions and is rewording the provision, now 211.165(f), so that it more clearly permits reprocessing of rejected materials.

398. Several comments argued that proposed 211.165(g) should be worded to allow use of materials that deviate from standards and specifications that have no bearing on the quality of the drug product. The Commissioner believes that it is clear in the context of this section that the standards and specifications referred to are those for acceptance or rejection.

As stated elsewhere in this preamble, the standards for acceptance or rejection must be realistic while at the same time appropriate to assure the quality of the drug product. Any deviation from such standards is not acceptable. On the other hand, there is no requirement that a firm establish specifications or standards that do not relate to the quality of the drug product.

STABILITY TESTING

399. One comment on 211.166(a) questioned the need to prepare a written testing program to assess stability characteristics of products such as borax and boric acid because methods of assay and analytical procedures for these materials are well documented. The Commissioner notes that the written testing program includes more than just a description of the method by which a drug product is tested. It includes all the requirements listed in this section. If the test method used is an official compendial method or other authoritative method, then it would be sufficient to refer to the source of the method to satisfy that part of the requirement for written procedures for the testing program.

400. Several comments requested that the word "statistically" be removed as a modifier of "valid estimates of stability" in 211.166(a)(1). The Commissioner is modifying the

final regulation to clarify that the statistical criteria apply solely to sample size and test intervals to provide assurance that every batch of drug product produced has essentially the same stability characteristics.

401. Several comments requested insertion of the words "where feasible" after the words "reliable, meaningful and specific test methods" in 211.166(a)(3). The Commissioner believes the phrase "where feasible" would suggest serious gaps in analytical methodology in drug manufacturing operations that in fact do not exist. The manufacturer has a responsibility to use test methods most suitable to assess the stability characteristics of his drug products.

402. Several comments requested the use of container closure systems for a stability testing program that are "similar" to the marketed container/closure system rather than the "same." The Commissioner concludes that the container-closure system should be the same as the one used for marketing the drug product with regard to attributes that could possibly affect stability.

403. A comment on 211.166 requested that the importance of stability testing of bulk active ingredients be emphasized because many manufacturers feel that stability testing applies only to finished dosage forms. The requirement in these regulations for performing stability tests applies only to "drug products," which are defined in 210.3(b)(4) as finished dosage forms.

Therefore, it would not be appropriate to include a requirement for bulk drugs in these regulations. The Commissioner believes that appropriate stability testing for active ingredients is a requirement under section 501(a)(2)(B) of the act because all drugs, including bulk drug ingredients, must be produced in conformance with current good manufacturing practice.

Stability testing of bulk drug ingredients is a current good manufacturing practice, and the Commissioner will propose to include it in the projected CGMP regulations for bulk drugs.

404. One comment requested the exemption of extremely stable compounds, such as calcium carbonate, from the stability testing requirements. The Commissioner denies the request for the exemption. The stability of an active ingredient is not the only characteristic that should be examined in a stability testing program. A product may leach compounds from its packaging materials or be affected by heat or moisture in ways which could be detrimental to product quality without affecting its strength.

405. A comment asked whether the reference samples in 211.166 can be taken from regular production batches for stability testing programs. The Commissioner notes that 211.166(b) clearly states that reference samples must be taken from regular production batches for stability testing programs.

SPECIAL TESTING REQUIREMENTS

406. Several comments on 211.167(a) recommended that sterility and/or pyrogen testing for veterinary drugs be excluded as unnecessary. The Commissioner finds that this paragraph does not establish whether any class of drugs is to be sterile and/or pyrogen free. The requirements of 211.167(a) relate to drug products that purport to be sterile and/or pyrogen free.

407. One comment said an apparent conflict existed between 211.167(a) and proposed 211.165(d)(2), which would require destructive testing of the batch for the characteristics of sterility and/or pyrogenicity. The Commissioner notes that proposed 211.165(d)(2) specifically acknowledged that it would not be appropriate to destructively test the entire batch. Section 211.165(d) is reworded in the final regulation, with

paragraph (d)(2) deleted, and the Commissioner sees no conflict between it and 211.167(a).

408. One comment on proposed 211.167(b) said collaborative laboratory studies have not established procedures for accurate and reliable testing for the presence of all types of foreign particles and harsh and abrasive substances. Alternative wording was suggested that would provide for such specifications and testing on an individual firm basis. Other comments recommended that the requirement be restricted to testing for metal particles, as is currently required by the compendia.

The Commissioner recognizes that tests for particles other than metal are generally not as precise as those tests for metal particles. The United States Pharmacopeia and FDA regulations for antibiotic ophthalmic ointments (21 CFR 436.206) contain requirements for testing for metal particles and limits for such particles. The majority of firms manufacturing ophthalmic ointments perform tests for other particle matter in addition to the U.S.P. or FDA required tests for metal particles.

The Commissioner considers it a current industry practice for manufacturers to reduce or control the harshness and/or abrasiveness of ophthalmic ointment drug products that may be caused by any particles, including the components themselves. Components may, for example, contribute to harshness and/or abrasiveness of the ophthalmic ointment because of crystalline size and shape. The Commissioner is retaining provisions for appropriate testing other than those for metal particles. Some firms employ a subjective test for abrasiveness, such as rubbing a sample of the drug product between the fingers; the Commissioner does not consider this type of test adequate, however, unless the individual is qualified to conduct this organoleptic test.

409. One comment called attention to situations in which the coating of tablets in different coating pans during

the manufacturing process may affect the release pattern and suggested that each pan be sampled, tested, and accepted or rejected on an individual basis.

The Commissioner recognizes the significance of proper coating in relation to its effect on the release pattern of active ingredients. Section 211.110 requires in-process controls to validate the performance of processes that may cause variability in the in-process material and the drug product. Sections 211.165 and 211.167 also require satisfactory conformance to finished drug product specifications.

While he believes this to be adequate at this time, the Commissioner will consider the need for more specific requirements, either in the general CGMP regulations or in specific CGMP regulations for sustained release drug products or drug product tablets, because of unique problems that may be presented by tablet coatings, especially if active ingredients are in such coatings.

RESERVE SAMPLES

410. Numerous comments on 211.170(a) said reserve samples of components need not be kept for 2 years beyond the expiration date of the products containing them. There were numerous alternatives suggested, ranging from 2 years after use of the component to 1 year after the expiration date of the last drug product containing the component.

The Commissioner has concluded that the requirement for retention of samples for 2 years beyond the expiration date is not necessary. The 2-year requirement had been proposed to make the period consistent with the present alternative requirement of 2 years after distribution of the last drug product incorporating the component, if longer than a period of 1 year after the expiration date.

The Commissioner is revising the final regulation in 211.170 to require retention for 1 year after the expiration date of the last lot of drug product containing the component. Where no expiration date is required, such as for human OTC drug products meeting the criteria for exemption under 211.137, the retention period is 3 years after distribution of the last drug product lot containing the active ingredient.

The 3-year retention period also applies to the reserve sample of the drug product under 211.170(b) and to retention of records and reports in 211.180. Appropriate revisions are made in the final regulations.

411. Several comments recommended that hazardous and unstable materials be exempt from the reserve sample requirement in 211.170(a). Other comments suggested that inactive ingredients also be exempted. The Commissioner has concluded that storage of some types of materials may constitute an unnecessary burden or a safety problem. The section, as revised, will eliminate retention of inactive ingredients.

He believes that deletion of retention requirements for inactive ingredients will eliminate most of the objections regarding hazardous and unstable materials; most of those materials cited by respondents are used as inactive ingredients. For those active ingredients that may be hazardous, though, the Commissioner concludes that the need for retaining samples of such active ingredients outweighs potential problems of storage.

412. A comment suggested that the word "appropriate" be inserted before the word "tests" in 211.170(a) because some tests require extremely large quantities of component. The Commissioner understands this comment to object to maintaining reserve samples when the amount of material needed to conduct the required tests is large.

The Commissioner has concluded that the advantages of keeping such amounts of active ingredients outweigh any expected burden. He advises that this is an existing CGMP requirement.

413. One comment said it is not necessary to retain reserve samples of multiple shipments of the same lot number of components. The Commissioner rejects this comment. Conditions of transit and storage can vary from shipment to shipment; such variable conditions can produce variations in the lots of different shipments.

414. Several comments on 211.170(b) said the requirement for inspecting reserve samples of drug products annually is unnecessary in consideration of the requirement for stability studies and, further, that deterioration normally cannot be detected by inspection. Other comments said FDA should clarify its intent whether or not inspection was meant to require complete testing and whether such testing would be required if such would affect the integrity of the sample.

The Commissioner has concluded that the requirement for annual inspection is sound. Stability studies would not, in the usual sense, provide an opportunity for evaluating stability on a batch-by-batch basis. The intent of the regulation is not to require complete testing on each batch of reserve sample on an annual basis, but rather to require examination, such as would be done visually, and 211.170(b) is revised to so state.

The Commissioner recognizes that such examination would not provide the type of assurance that could be obtained by complete analysis, but the burden that complete testing would place on the industry would be unreasonable and unnecessary considering the requirements for establishing stability. The Commissioner is also revising 211.170(b) to require annual inspection only if it can be done without affecting the integrity of the sample.

415. One comment said the amount of paperwork could be reduced if only samples that were found defective during annual inspection were recorded on the individual product record. The Commissioner does not intend that there be a requirement for recording the results of examination required by this paragraph in the individual batch record for the product, if that is what the comment suggested. A record of samples must be kept so that test results can be correlated with each batch and the test results kept with other stability data.

416. Several comments said the requirement for retention of reserve samples in the same container-closure systems in which they are marketed is impractical in the case of very large or bulk containers. The Commissioner has concluded that there are instances, for example those involving very large or bulk containers, where it would be impractical to store reserve samples in the same size containers as is used for the marketed product.

Although the Commissioner finds that the same immediate container-closure system is preferred for storage of the reserve sample, he is revising the final regulation to allow the use of an immediate container-closure system having essentially the same characteristics as the marketed container.

This means, for example, that one size container may represent several sizes from the same batch, provided all containers were essentially the same except for size. The storage requirements for reserve samples differ slightly from the storage requirements for stability study samples in 211.166 because to obtain accurate stability data it is essential to duplicate the conditions that could affect stability.

LABORATORY ANIMALS

417. A comment said this section (211.173) should be deleted because the Laboratory Animal Welfare Act, enforced

by the Department of Agriculture, already regulates the care and use of laboratory animals.

The Commissioner notes that the CGMP requirements for the maintenance and control of laboratory animals are intended to assure that animal test results are valid in that the results have not been affected by the use of animals that may have been exposed to adverse environmental conditions.

The identification and maintenance of adequate records on animals are likewise intended to assure the validity of the test results. The intent of the Animal Welfare Act (7 U.S.C. 2131-2155) is, among other things, "to insure that certain animals intended for use in research facilities * * * are provided human care and treatment." Regulations implementing that act are quite detailed, but do not expressly deal with the two items of most immediate concern for drug quality purposes.

The user of such animals for drug testing would, therefore, be required to comply with both the CGMP requirements of the act and the requirements of the Animal Welfare Act.

418. A comment said because not all manufacturers have animal facilities, the regulation should make it clear that 211.173 applies only when animals are maintained for test purposes. The Commissioner believes that it is clear that if animals are not used, the section does not apply. The intent of the section is not to require the use of animals, but rather to set standards applicable when animals are used. Therefore, the Commissioner sees no need to accept this comment.

419. One comment argued that the requirement for physical separation of animal maintenance facilities would be an undue hardship because it does not allow for flexible use of space by the manufacturer. The Commissioner notes that 211.173 does not speak of physical separation.

The degree of separation in maintenance and control of animal facilities should be sufficient to assure that animal test results are valid in that the animal facilities do not contribute contamination to the drug product or the manufacturing facilities.

420. A comment said identification and recordkeeping for use of individual animals is unnecessary if the animal is used only once. The Commissioner rejects this comment. Identification of each animal and adequate recordkeeping are a basic part of any biological test in order to assure accurate results.

Even rodent species used only once should be accounted for on an individual basis to prevent inadvertent reuse, which may result in inaccurate test results. The Commissioner has dealt at some length with problems uncovered in reviewing drug testing in animals (see proposed regulations for good laboratory practice published in the FEDERAL REGISTER of November 19, 1976 (41 FR 51206)).

PENICILLIN CONTAMINATION

421. A comment on 211.176 said that because zero penicillin levels are required, raw material suppliers should certify that their products are penicillin free. The Commissioner believes that, although drug manufacturers can at their own initiative request such certification from suppliers, FDA should not require suppliers of raw materials to test every lot of raw materials for penicillin, even when no reasonable possibility exists that they have been contaminated with penicillin. This would place an unnecessary burden on suppliers.

422. A comment said FDA is not qualified to test for penicillin contamination because FDA receives multiple samples in the same cartons, and they are kept together in the same room in the testing laboratory. The Commissioner has concluded that there is no basis for this comment.

Samples for cross-contamination testing are received by the FDA laboratory in sealed containers that are individually placed in sealed plastic or paper bags. Analyses for penicillin cross-contamination are conducted in a laboratory facility separate from that used for penicillin certification analyses.

Positive and negative controls are run, and the analyses are conducted in laminar flow hoods under positive pressure. Thus, FDA is quite capable of determining the presence or absence of penicillin contamination.

XV. RECORDS AND REPORTS

GENERAL REQUIREMENTS

423. Some comments on 211.180(a) objected to maintaining production, control, and distribution records for 2 years after the expiration date of the batch. They mentioned the increased cost of record storage and noted that adverse reactions, complaints, recalls, and other phenomena justifying record storage generally occur shortly after beginning distribution.

Various time periods were recommended as alternatives. Several comments suggested a retention period of 2 years after the batch was approved for marketing. The Commissioner finds that these records must be available for review for a reasonable time period beyond the expiration date of the products covered in the records to provide an opportunity for appropriate followup of any complaints or other adverse reports received during the entire marketing period. In reconsidering the extent of such retention period in light of the comments, however, the Commissioner has determined that a 1-year period following the expiration date will generally be adequate to assure that the records will be available for review if necessary.

In the case of certain OTC drug products not being required to bear an expiration date because they meet the criteria for exemption under 211.137, the record retention period is 3 years after distribution of the batch. This 3-year period is considered appropriate because the exemption is based on an assumption that such products will be used within 3 years after manufacture.

Therefore, record retention for 3 years after distribution should be adequate to cover the time period during which records are most likely to be needed. The Commissioner recognizes that these final regulations will require retention of records beyond that currently required in the CGMP regulations. The CGMP regulations require the retention of certain records, e.g., batch production and control records, for time periods that are based on the distribution of the lot or, where applicable, the expiration date of the batch.

The current regulations do not clearly specify the record retention period for other records. For some firms, the retention period for records will not change as a result of this regulation, as their practice is being incorporated in these regulations. In other cases, however, these regulations will require retention of records for a period of time longer than the minimum retention period specified in previous CGMP regulations.

With specific regard to physical space for the storage of records, the Commissioner advises that the regulations do not generally require retention of original records, and that retention of suitable true copies in other forms such as microfilm is permitted. The Commissioner believes that, in keeping with modern business practices, there are many record retention systems that would fulfill the intent of the record retention provisions. Section 211.180(d) of the final regulations specifically provides for this flexibility.

424. One comment said 211.180 should be deleted because section 703 of the act prescribes the maintenance of certain records that show the movement of articles in interstate commerce and does not mention the retention of records as described in 211.180. The Commissioner disagrees with this comment. Section 703 of the act permits FDA access to records of interstate shipment in the possession of carriers (i.e., transportation companies) or other persons receiving or holding food, drugs, devices, or cosmetics in interstate commerce. The provisions of section 703 do not apply to the manufacturers of drug products insofar as records of production are concerned.

425. One comment suggested that retention of records for components that have an indefinite stability or components that are used only occasionally to produce batches of drug products be excluded from 211.180(b). The Commissioner rejects this suggestion. The retention period is related to the expiration dates of the batches of drug products containing that batch of the component in order to assure that the records would be available for review during the marketing of the drug products and for a reasonable period thereafter.

The Commissioner seriously questions whether any drug product can be considered indefinitely stable or would in fact carry an expiration date that would require record retention for an extraordinarily long time. Finally, the Commissioner notes that because the manufacturer has discretion to establish an expiration date that is less than the actual stability of the drug product, the manufacturer also has reasonable control over the periods during which he must retain records.

426. One comment said 211.180(b) is overly inclusive and should be reworded to include only those components that come in actual contact with the drug product. The Commissioner is unclear on the use of the word "component" in this comment. The definition of "component" appearing in the CGMP regulations would only include ingredients intended

for use in the manufacture of a drug product, including those that may not appear in the final product. Section 211.180(b) limits records to components actually incorporated in the drug product.

Thus, it seems obvious that the regulations only apply to components "that come into actual contact with the drug product" as requested in this comment. Therefore, the Commissioner cannot agree that the requirement as proposed is too extensive, and he sees no justification for revisions in the language in this paragraph.

427. Some comments suggested that reference to drug product containers and closures be deleted because these items are not subject to deterioration. One comment suggested that the requirement be retained for parenterals only. The Commissioner does not agree that reference to container/closure record retention should be deleted because they are not subject to deterioration.

The Commissioner is aware that some container/closure systems are subject to deterioration and there are other possible problems with containers and closures that may adversely affect the drug product. The purpose and intent of recordkeeping requirements is to be able to trace the complete history of a batch and thereby enable a firm and FDA to investigate fully any problems that may arise with either the product, the container/closure system, or both.

Complete records would also make possible a determination of whether or not other batches or other drug products are or could be involved with the same problem. The failure to have these records available for any investigation could prevent the resolution of an undesirable condition. Therefore, the Commissioner is retaining this requirement to include all drug product containers and closures.

428. A comment on 211.180(b) was submitted regarding the retention of records for compressed medical gases. The comment, which assumed that expiration dating would not be required for compressed medical gases, requested a retention period to be some logical and meaningful period. The Commissioner finds that there is no justification for excluding retention of records required for compressed medical gases under this paragraph. The Commissioner has also decided to require expiration dating for medical gases.

428a. Several comments objected to reference to recordkeeping and record inspection requirements in proposed 211.180 (c) and (d) insofar as they apply to over-the-counter (OTC) drugs and to "not new" drugs. These comments pointed out that section 704(a) of the act authorizes inspection of records regarding prescription drugs only and inspection of records regarding research data only on "new drugs" subject to section 505 of the act.

One comment cited extensively from the legislative history of section 704 of the act indicating a congressional intent to limit the scope of inspection granted to FDA. The Commissioner has reviewed the legislative history of the 1953 amendments (Pub. L. 83-217), which originally enacted section 704(a) of the act, as well as the amendments contained in the Drug Amendments of 1962 (Pub. L. 87-781 (1961)), which extended FDA's authority to review records for prescription drugs under the mandatory inspection authority of section 704 of the act.

He finds that Congress did not include in the scope of the inspection authority under section 704 of the act (and its concomitant enforcement section under section 301(f) of the act) authority to inspect records regarding the manufacture of OTC drug products or research data on prescription drugs that are not "new drugs" as defined in section 201(p) of the act.

The Commissioner also finds, however, that section 704 of the act does not exhaust the varieties of inspections that FDA may

be authorized to make regarding such drug products. Manufacture of any drug product without compliance with current good manufacturing practices renders the product adulterated a prohibited act under section 301(b) of the act and a Federal crime under section 303 of the act.

Thus, if FDA had reliable information indicating that an OTC or old drug product was being manufactured in violation of current good manufacturing practice, the agency could obtain a search warrant that would authorize FDA to inspect manufacturing records regarding the drug product to seek evidence regarding the alleged criminal offense.

A second type of FDA inspection into OTC drug production records would be in conjunction with inspections under Government-wide Drug Quality Assurance Programs. Manufacturers contracting to provide OTC drug products to the Department of Defense, the Veterans Administration, or the Public Health Service must, as a condition under those contracts, permit FDA to inspect the plant, facilities, and records regarding the product to determine compliance with the Federal Food, Drug, and Cosmetic Act.

If the manufacturer withdraws his consent for FDA to inspect, FDA will decline to accept the product on behalf of the purchasing Government agency, and if that agency so decides, the contract may be terminated.

A third example of an inspection authorized under the act is found in section 505(j)(2) of the act where a manufacturer must permit inspection of records regarding new drugs which are required under section 505(j)(1) of the act; failure to do this is a prohibited act under section 301(e) of the act. It is conceivable that an NDA for an OTC drug would be subject to recordkeeping requirements regarding manufacturing activities, and if so, FDA could inspect these records, notwithstanding section 704 of the act.

This does not necessarily identify all circumstances in which FDA may be authorized to make an inspection of records regarding the manufacture of an OTC drug product or research data on "not new" drugs. See, generally, Horton, "Warrantless Inspection Under the Food, Drug, and Cosmetic Act," 42 G.W. Law Rev. 1089 (1974).

The purpose of 211.180(c) is to assure that all appropriate records were properly collected, indexed, and held at the site where an inspection would occur so that, in the event of an authorized inspection by FDA, these records would be readily reviewable by the FDA inspector.

Otherwise, an unnecessary delay may occur if the manufacturer had to locate and collect the appropriate records for an inspection. It is not the intent of these paragraphs of the regulations to compel a manufacturer to submit to an inspection that was not legally authorized. To clarify this, the Commissioner is inserting the word "authorized" before the word "inspection" in 211.180(c).

429. Several comments objected to the requirement that records be readily available at the establishment where such recorded activities take place on the grounds that most firms with multiple facilities maintain central record storage facilities and that compliance with 211.180(c) would require needless and unnecessary duplication of the records and storage facilities.

These comments suggested that provision be made for central record storage sites, provided that the requested records be made available in a reasonable period of time. The Commissioner does not agree with the contention that keeping these records or copies of them at the establishment where the activities took place would be unnecessary and would require needless and unnecessary duplication of the records and facilities.

He is of the opinion that most firms today keep the records or copies of them at the site where they were generated. These critical records must be available to both plant personnel and FDA for review. To require that plant personnel and FDA investigators place orders for specific records to another facility and then wait for delivery would not be prudent. There is the distinct probability that operating under these circumstances would greatly extend the time needed to conduct an investigation of a problem or to conduct the required inspections.

The Commissioner does believe, however, that records that can be immediately retrieved from another location by computer or other electronic means meet the requirement of being readily available at the establishment. The final regulation includes this provision. As the Commissioner stated in reply to other comments regarding record storage, these regulations do not preclude the use of other record storage systems, such as microfilm or microfiche.

Where other systems are employed there must be associated capability for viewing and copying. The final regulations include a new 211.180(d) to clarify these provisions.

430. One comment suggested that the regulation provide guarantees that the FDA investigator will not copy these records or if they are copied, that they will not be released under the Freedom of Information Act. The Commissioner cannot agree with the first suggestion.

There are many instances where the investigator who makes the inspection does not have the time to review records at the establishment for all of the facets involved. In addition, this suggested provision would result in an inordinate expenditure of FDA resources to provide adequate time for a complete review of the records at the plant site.

The Commissioner believes that true reproduction of records, compared with handwritten copies, assures their authenticity and decreases inspectional time. While the copying of appropriate records has always been implicit in CGMP regulations, there have been instances where investigators were restricted by manufacturers to handwritten copying of the records.

Therefore, 211.180(c) is being amended in the final regulation to clarify that records are subject to copying during the course of an inspection. The Commissioner also rejects the respondent's suggestion that documents not be released under the Freedom of Information Act.

The Commissioner is required by law to release documents in his possession unless they contain information or are of such a nature that a request for release could be denied. In this regard, the Commissioner specifically refers to the FDA regulations describing public disclosure of "trade secret" information in FDA files (21 CFR Part 20, particularly 20.61).

431. Numerous comments objected to 211.180(e) (proposed as 211.180(d)) on the grounds that the requirement for the generation of a written summary is not current practice and would have an unnecessary inflationary impact without any noticeable effect on improving the quality of drug products in general.

Some of these comments argued that the proposal did not specify what data were to be summarized. Other respondents questioned the authority of the FDA to require these summaries. Numerous additional comments were submitted suggesting that these summaries be prepared "when necessary" or "when needed." Several other comments objected to the required retention period.

The Commissioner has carefully considered the extensive comments regarding the proposed requirements for written

summaries and concludes that revisions in this paragraph are justified. The purpose is to provide reliable procedures for a manufacturer to review the quality standards for each drug product. The Commissioner agrees that mechanisms other than written summaries may be appropriate for such evaluation.

Therefore, the final regulation is amended to require that manufacturers establish their own written procedures for annual evaluation of the quality standards for each drug product.

While not specifying what review mechanism must be used, the Commissioner encourages the use of written summaries as one practical means of drug product review. The Commissioner believes that some manufacturers are currently using such written summaries to good advantage in establishing drug product profiles.

432. Several comments objected to 211.180(f) (proposed as 211.180(e)) on the basis that it is an unwarranted intrusion into corporate duties and responsibilities, and adherence to this requirement would not affect the integrity of the drug product. Some of these comments suggested an exclusion for small businesses because the corporate officials would be writing themselves reports.

Still others suggested limiting these reports to significant findings. The Commissioner believes there are sound reasons for this proposed requirement. From time to time it has been the agency's experience that corporate officials have not been advised of potential or real adverse conditions brought to light either by the firm's own quality control system or by FDA.

As a result, corrective actions have not been instituted where they might have been, had company officials been aware of such conditions. Correspondence from FDA to firms regarding

inspectional findings and recalls is directed to top officials as a matter of policy, but not all conditions specified in 211.180(f) are the subject of inspections or recalls, and even in the case of inspection and recalls there may be a period of time before FDA correspondence which deals with the subject is issued.

The Commissioner does not believe that the requirements of 211.180(f) are burdensome and is confident that the concept of keeping officials informed of such situations as specified in 211.180(f) is, for the most part, current industry practice. The Commissioner rejects the argument that the requirements of this paragraph are an unwarranted intrusion into corporate duties. They will provide added assurance that efforts are being directed toward the prevention and/or correction of conditions that could effect the quality of the drug product.

Moreover, responsible officials already have very rigid legal duties to be aware of, and to take action upon, conditions contributing to drug adulteration (United States v. Park, 421 U.S. 658, 1975; United States v. Dotterweich, 320 U.S. 277, 1943).

In view of the comments, however, the Commissioner is deleting the proposed requirement regarding routine quarterly written reports in order to allow manufacturers flexibility in establishing procedures to keep appropriate management fully informed as to important matters involving possible quality control problems.

In addition, the final regulation provides an exception for officials, whether in large or small firms, who are personally involved or immediately aware of investigations, recalls, reports of inspectional operations, and regulatory actions relating to CGMP regulations.

EQUIPMENT CLEANING AND USE LOG

433. Several comments on 211.182 and 211.186 recommended that the requirement for signatures be deleted or modified to provide for initials, or other specific employee identification, e.g. an employee number. The Commissioner is persuaded that the requirement for a full signature may not be warranted in view of the space that would be required in the records and the burden of continually writing a full signature on records that are repetitive.

For less repetitive type of records, such as master records referred to in 211.186, the Commissioner has decided to retain the requirement for a full signature. The Commissioner rejects the suggestion that a distinctive employee number be allowed because it would detract from the concept of personal involvement. Numbers, in the Commissioner's opinion, may be easily recorded by persons other than those who actually perform the function.

434. Some comments suggested that the word "strength" be deleted from 211.182 as superfluous because this information is readily derived through the lot or batch number. The Commissioner agrees that the word "strength" can be deleted. The remaining required information is sufficient to identify the batch.

435. Several comments objected to the requirement in 211.182 that an individual written record of all equipment cleaning and maintenance would have to be double-checked and signed. This requirement could include logs for stirrers, scoops, and ladles. The Commissioner agrees that this requirement, as proposed, could be construed to include such items as ladles, stirrers, scoops, spoons, and spatulas.

Therefore, the word "major" is being inserted before "equipment." This change does not affect the responsibility of assuring that all utensils and other equipment are properly and adequately cleaned before re-use, but only documentation of such activities.

436. One comment on 211.182 doubted the need for routinely double-checking cleaning and maintenance. It argued that this would require the checkup person to be present during the operation. A second comment said the requirement for checking routine maintenance would be overly burdensome.

The Commissioner notes that the purpose of this requirement is that a second person determine that appropriate cleaning and maintenance was performed. He does not believe that this necessitates that the person doing the checking be present during the entire operation. Changes in the final regulation clarify this intent and also exclude from the required checking routine maintenance activities such as lubrication and adjustments.

437. Several comments on 211.182 objected to keeping logs inasmuch as the information is readily available in other records, such as the batch record.

The Commissioner rejects this view because in most instances batches are not processed consecutively on any one piece of equipment. If the practice were not followed and one attempted to determine the chronological use of a particular piece of major equipment to ascertain, e.g., whether several batches were affected by a malfunction, a burdensome review of numerous batch records would be necessary.

438. Some comments said logs required in 211.182 are not necessary when equipment is dedicated to a single product. The Commissioner agrees that if equipment is dedicated to the manufacture of one product, the requirement for individual equipment logs would not be necessary, provided that lots or batches of such products follow in numerical order and are manufactured in numerical sequence. In such cases where the use of dedicated equipment is employed, the records of cleaning, maintenance, and use shall be part of the

batch record. The Commissioner is revising this section accordingly.

439. One comment said 211.182 is an unnecessary burden on the manufacturer who places reliance on the drug product's final testing. The Commissioner is aware that dirty or poorly maintained equipment can introduce characteristics to a drug product that may not be detected by final examinations. Moreover, it is in the manufacturer's interest as well as the public's to prevent quality assurance problems, rather than simply detect them. Therefore, the Commissioner rejects this comment.

440. Comments objected to the requirement for one log for each piece of equipment containing the information regarding cleaning and maintenance when a portion of the cleaning or maintenance may be performed either at another location or by a different department. The Commissioner notes that it is not the intent of this section to limit the number of logs for each piece of equipment to one. The intent is that there be one or more logs for each major piece of equipment which, in their entirety, contain the information required by this section. The Commissioner does not believe the section implies otherwise.

COMPONENT, DRUG PRODUCT CONTAINER, CLOSURE, AND LABELING RECORDS

441. Several comments requested an exemption of veterinary drug products from the requirements in 211.184 (a) and (c). For drug product containers and closures, it was also suggested that the section be modified to indicate that the requirements regarding product containers and closures should apply only to the drug products intended for human use.

The Commissioner rejects these comments. He sees no sound arguments that drugs intended for veterinary use should be subjected to lesser controls than human drug products.

442. Several comments objected to the proposed requirements in 211.184(a) for the lot history of drug product containers and closures. Comments were that existing controls product containers and closures are sufficient and in some instances the supplier's lot number and the location of the manufacturer are not known.

Another comment expressed concern that reporting of the name and location of the prime manufacturer "if known" was not sufficient and such reporting should be mandatory. The Commissioner cannot agree that the information relating to the lot history of drug product containers and closures is not important in providing prompt and accurate identification of such lots, when necessary.

Generally, the required information is already available and recorded by most manufacturers, but may not have been previously organized in such a manner as to facilitate identification of drug product containers and closures. The Commissioner acknowledges that, occasionally, information such as the supplier's lot number or location of the manufacturer is not known.

The proposed regulation already provided for the instances where the name and location of the prime manufacturer, when different from those of the supplier, is not known, and the final regulation also takes into account that a supplier's lot number may not always be available. This modification, however, does not diminish the control over such drug product containers and closures by the drug manufacturer. The receiving code, specified in 211.80, will serve to identify the received lot to the drug manufacturer. The Commissioner encourages all suppliers to adopt batch or lot identification to aid in locating components, drug product containers, and closures in the event it becomes necessary to do so to protect the public health.

About the comment for mandatory recording of the prime manufacturer in all cases, the Commissioner concludes that such a requirement is not necessary. Because such information is usually readily available, however, and may be useful to the manufacturer in considering the suitability of suppliers or allow for tracing the complete history of the component, container, or closure, it should be recorded when available.

443. One comment on 211.184(b) recommended substituting the phrase "subsequent disposition assigned to the material" for the phrase "conclusions derived therefrom" in the last line of this paragraph because under the sections cited in the proposed paragraph, the only possible decisions are release, restrict, reprocess, or reject.

The Commissioner cannot agree with this comment and believes the comment may have misinterpreted the proposed requirement. Results of tests or examinations required under the sections cited in this paragraph are clearly to be included, but all tests and examinations must be considered. There are a wide range of conclusions that may be drawn from results of tests or examinations.

For example, a test failure resulting from improper testing procedure would be recorded, but the lot would not necessarily be rejected based on that one improperly performed test. The Commissioner finds that this paragraph should be finalized as proposed.

444. Many comments addressed 211.184(c). Most agreed that an inventory record and reconciliation for drug product components was appropriate, but objected to inventory records and reconciliation for drug product containers and closures. Others contended that inventory records, but not reconciliation, were also appropriate for drug product containers and closures.

Arguments were primarily that recordkeeping to this extent was unnecessary, burdensome, and not current practice. Some comments were concerned that extensive records and reconciliation would be required for packaging materials such as cotton filler material used in packaging tablets and capsules.

Several comments recommended changes in the proposed language that would clearly require that the inventory record be sufficient to establish the batch or lot of drug product in which component, drug product container, and closure are used. The Commissioner has reconsidered the need for individual inventory records and reconciliation of the use for components, drug product containers, and closures.

He finds that individual inventory records are necessary to provide an adequate history regarding the use of components, drug product containers, and closures. To clarify the intent that such inventory records are intended to allow for determination as to the batch or lot of drug product associated with the recorded inventory, the Commissioner is modifying the proposed wording in this section (211.184(c) and in 211.188(g)).

The Commissioner agrees with the comments that reconciliation of the use of each lot of drug product container and closure should not be required. Although there are instances where such reconciliation could be valuable to the drug manufacturer, it should not be mandatory for all drug products and all drug manufacturers.

The CGMP regulations elsewhere provide considerable control over the approval and use of drug product containers and closures. Because of the more critical nature of the ingredients on the other hand, each drug product component must be inventoried and its use reconciled in order to provide added assurance of product integrity.

The Commissioner emphasizes that this section does not pertain to all packaging materials, but only drug product containers and closures. Thus, individual inventory records for packaging materials such as cotton filler and package liners are not required under this section, although records regarding the receipt, examination or testing, and disposition for packaging materials generally are required in 211.122, particularly in paragraph (c).

445. One comment objected to 211.184(d) on the grounds that it could be interpreted to require each person on the manufacturing line who makes an inspection to record that inspection as it is made. The comment recommended deleting the word "all" from the paragraph. The Commissioner finds that this paragraph is intended to provide for the documentation of the examination of labeling as required elsewhere in the CGMP regulations.

To eliminate the possibility of misinterpretation, 211.184(d) is revised by substituting the words "the examination" for the words "all inspection" to conform more closely to the language used elsewhere. In considering the final regulation, the Commissioner finds that a new 211.184(e) is desirable to clarify that records regarding the disposition of rejected drug product containers, closures, and labeling must be maintained.

MASTER PRODUCTION AND CONTROL RECORDS

446. One comment noted that the phrase "master production and control records" as used in 211.186(a) was not limited to "appropriate master production or control records" as in 211.188(a), and requested clarification in regard to use of the word "appropriate." The word "appropriate" in 211.188(a) is intended to denote the master production or control record that is appropriate for the particular batch for the drug product. The Commissioner believes both paragraphs as written are clear in this regard.

447. Several comments argued that the "full signature, hand written" is not necessary and that the paragraph should be changed to allow for other means of identifying the persons who prepare and check the master production or control cards, such as initials, registered initials and/or signature stamps.

The Commissioner believes the requirement for a full signature is appropriate when applied to master records. In the past, FDA has on occasion found instances where firms could not identify the person or persons whom the initials were intended to represent. Further, the Commissioner does not believe this requirement to be burdensome because master production and control records in most cases would be infrequently established or changed.

448. One comment proposed acceptance of other validating techniques in the first sentence of 211.186(a) on the grounds that verification can be accomplished by machine. The Commissioner is not aware of how master production and control records can be totally prepared and verified by machine.

Although calculators or computers might assist in preparation and verification by aiding the persons involved, the initial information would have to be fed into the calculator or computer by a responsible person, and a second responsible person would have to verify that the hard data fed into the machine were valid.

Where appropriate, the use of automated equipment and computers is allowed under 211.68 provided hard data are kept of certain records such as master production and control records.

449. One comment said the words "where appropriate" should be inserted after "strength" in the first line of 211.186(b)(1). The Commissioner rejects this comment

because it is appropriate to include the strength of the drug product on the master production and control records.

450. One comment said 211.186(b)(4) should be revised to require use of the metric system of measurement only. The Commissioner rejects this comment. While the metric system is used to a great extent in the drug manufacturing industry, a requirement for conversion to the metric system as the sole method of measure could be an unnecessary burden upon industry at this time.

Such a requirement may be imposed in the future by the Commissioner, in keeping with national laws on conversion to the metric system and good manufacturing practice.

451. One comment said the requirement for 211.186(b)(4) for using the same weight or measure system should be deleted or revised to allow firms to change the master formulas gradually over a period of years or as the drug product is reformulated. The Commissioner believes that the large majority of drug firms already comply with this requirement.

The Commissioner notes that the effective date of this final regulation allows sufficient time for the remaining firms to comply with this section and therefore rejects the suggestion that firms be allowed to change their systems over a period of years.

452. One respondent recommended that the requirement for "using the same weight system" in 211.186(b)(4) should not be applied to veterinary drugs because these are often produced in large volumes or masses. The Commissioner finds no justification for exempting veterinary drugs from this requirement.

The fact that large volumes or masses are involved is not a convincing argument that the requirements for use of a

consistent measurement system should not apply to the manufacture of veterinary pharmaceuticals. Drug products for human use are also often manufactured in large volumes or masses.

453. One comment on 211.186(b)(7) said repetitious calculation of percentage of theoretical yield adds nothing to the integrity of the product. The Commissioner rejects this comment. The regulation does not require "repetitious" calculation of theoretical yield; instead, one calculation must be made part of the master production and control records, together with appropriate tolerances from this calculation beyond which an investigation for manufacturing errors would be required.

454. One comment said the theoretical yield percentage, which if exceeded would require an investigation under 211.192, should not be included in the record as required in 211.186(b)(7) because the investigation is the responsibility of the quality control unit. The Commissioner does not understand the reasoning behind this comment.

The fact that this information appears in master or batch records does not displace responsibility of the quality control unit.

455. One comment said the requirement in 211.186(b)(7) for a statement of theoretical yield does not take into account that there is sometimes a shortage in the actual yield because a manufacturer may discard a portion of a batch due to a problem with the "pharmaceutical elegance" of the product.

The Commissioner sees no reason to accept this comment. The purpose of the theoretical yield requirement is to serve as an indicator of a possible error when compared to the actual yield. If the manufacturer can account for the shortage in the actual yield of the product by documenting that a definite portion of

the lot was discarded because of its inelegance, the regulations have been followed.

456. One comment argued that the label should be required to be maintained on file and not physically attached to the master production or control record. The requirement does not state that the label has to be glued or stapled to the master record, for example, if this is what the respondent means by "physically attached." Since 1963, the CGMP regulations have required that a specimen or copy of each label be included in the master production and control record.

This requirement is needed in order to make the master production and control record complete with respect to all aspects of processing, and should not be changed.

457. Several comments regarding 211.186(b)(8) and 211.188(b)(8) said lithographed bottles, cans, and ampules cannot be kept on file. The Commissioner notes that the final regulations provide that a "specimen or copy" be included in the master and batch production or control record. A photograph, photocopy, or other accurate reproduction will fulfill the intent of these sections.

BATCH PRODUCTION AND CONTROL RECORDS

458. One comment on 211.188 said batch production and control records should be permitted to be extensively simplified because lots are repetitive and are usually processed on identical equipment in an identical manner for months or years. The Commissioner notes that this comment fails to specify what simplifications are proposed.

The purpose of these regulations is to provide for a written system which, when followed, results in a reproducible high-quality drug product. The Commissioner believes that "simplifying" the batch and record controls by reducing the types of information required would have an adverse effect

upon the quality of the drug product and would not reflect current industry practice.

On the other hand, use of forms to ease the recording of information (without omitting any) would fulfill the provisions of this section.

459. A comment said there is no need to check a batch production and control record, as required in 211.188, if it is a photocopy reproduction of the master production and control record. Further comment recommended that the words "where necessary" be inserted after the word "accuracy" in the third line of 211.188(a). The purpose of this requirement is first of all to make sure that the correct master production or control record has been copied. Also while photocopying may be the most accurate and preferred means of producing a batch production and control record, no system is infallible.

For example, a spot or mark on the plate glass surface of the copier could result in the obliteration of a letter or the addition of a period onto the photocopy reproduction, and this might change the formula. The Commissioner believes that the checking, dating, and signing of a batch production and control record is always necessary to assure that such records are correct.

460. A comment said 211.188 should explicitly allow the use of batch production or control records produced by a computer. The Commissioner notes that 211.68 clearly permits the use of computers in the manufacture, processing, packing or storage of drug products. Section 211.188 does not limit the means by which a batch production or control record may be produced.

The Commissioner does not believe that repetitiously providing for the use of computers or any other means of reproducing batch production and control records in each section where it is applicable is necessary.

461. Several comments said 211.188 is unclear as to what records are encompassed in the requirements. Specifically, one asked whether the term "appropriate" in 211.188(a) allows a manufacturer to use a "manufacturing ticket" that does not contain all the information in the master production or control record. Although the Commissioner is not sure of the intended meaning of "manufacturing ticket," he notes that the word "appropriate" in 211.188(a) refers to the master production and control record for the size of batch, strength, and dosage form that is to be manufactured.

The term "appropriate" is not intended to allow a manufacturer to delete any pertinent information from the batch production and control record. As stated in this paragraph, the batch production and control record shall be "An accurate reproduction of the appropriate master production or control record, checked for accuracy, dated, and signed."

If a portion of the batch production record were sent to a particular department that is involved only in the operation covered by that portion of the batch record, the Commissioner would consider that practice to be consistent with the requirements of this section.

462. A comment said provisions should be made in 211.188 for batch production and control records only to the extent that each operation is performed by each establishment, because some operations such as packaging are often performed by another firm. The Commissioner advises that a new 210.2(b) is added to these final regulations to clarify the applicability of CGMP regulations to persons engaged in only some of the operations subject to these regulations.

463. Several comments said the words "and after" should be deleted from 211.188(b)(6) as requiring unnecessary and burdensome duplicative inspections. The Commissioner rejects this comment.

To prevent mixups and to reconcile the label count after packaging, it is necessary to inspect the premises after each packaging operation. It is also necessary to inspect before the next packaging operation because foreign materials other than those from a previous packaging operation could be introduced into packaging operations. For those packaging operations that are "back-to-back" with essentially no time interval, a single inspection will meet the requirement of 211.188(b)(6).

464. Comment on 211.188(b)(7) said the statement of percentage of theoretical yield should be ascertained only at the completion of compounding and packaging because some drug manufacturing processes are not complicated operations. The Commissioner concludes that this section will have to be applied in consideration of the complexity of the processing needed for each drug product.

The calculation of the percentage of theoretical yield only after completion of compounding and packaging may be appropriate in some cases where, for example, drug product manufacturing is not complicated. The revised final regulation should clarify that this flexibility is intended.

465. A comment said radio-pharmaceuticals should be exempt from the requirement in 211.188(b)(7), for developing theoretical yield data because its determination would involve reassay of the unused bulk radioactive material. The Commissioner believes that this section as revised in the final regulation responds to this comment in that the requirement applies at "appropriate stages" of processing. The Commissioner also notes that this section does not specify the tolerance levels for acceptance of actual yields.

Such levels will vary depending on the drug product being produced.

466. Several comments said the words "or if impractical, a label revision number," should be inserted after

"specimen" in 211.188(b)(8). The Commissioner rejects this comment. This requirement provides a ready means for production personnel to verify visually the processing record against what is actually being processed and provides a more complete record than a label revision number might furnish.

PRODUCTION RECORD REVIEW

467. One comment on 211.192 indicated that accountability is of more concern than actual versus theoretical yields. The concept of accountability is implicit in the use of theoretical yields and particularly in the comparison made between actual and theoretical yields. The material produced, considering accountable losses, is the actual yield. Comparison of the actual yield with the theoretical yield, i.e., what should have been produced, requires a determination of acceptability. The actual yield is acceptable if losses have been satisfactorily accounted for.

467a. One comment proposed replacing the word "all" at the beginning of 211.192 with "batch." The Commissioner agrees that the intent of this section is to require review of those records that directly relate to batch production and control. Therefore, the comment is adopted in the final regulation.

468. A comment described the quality control unit review of production and control records in 211.192 as an excessive requirement because it would include reviews of internal manpower or labor use records. The Commissioner does not intend that documents outside those which impact on drug product identity, strength, quality, and purity should be reviewed by the quality control unit for release purposes. The regulation is revised to clarify this.

469. One comment proposed that a single individual should certify that the review for quality control considerations required in 211.192 has been made. The Commissioner finds

that because of the wide variety of activities and operations which the quality control unit is responsible for approving or rejecting, a number of different methods of expressing or indicating approval or rejection may be appropriate.

For example, in some firms the "Director of Quality Control" may personally sign all approvals or rejections. In other firms, however, the "Director of Quality Control" may delegate this responsibility to subordinates. However, the Commissioner does not believe it is appropriate for him to dictate that specific persons be solely authorized to perform these functions.

LABORATORY RECORDS

470. One comment suggested revising 211.194(a) by inserting the word "required" before "test," because not all laboratory tests are germane in determining the product's acceptability. It was stated that some tests are primarily for informational purposes and should not be part of the records. The intent of this section is that laboratory records include data derived from tests that are necessary to assure compliance with established specifications and standards. The final regulation is revised accordingly.

471. Several comments suggested that the word "quantity" be deleted from 211.194(a)(1) because this information is contained in other records, and the requirement is excessive and of no value. The Commissioner rejects these suggestions because it would be pertinent, upon review, to determine whether the size of sample drawn is representative.

A record of the size of the sample drawn also allows for a reconciliation of the amounts used for each test with the amount of total sample. This could provide important information for any investigation that may be instituted following marketing of the batch or lot. The Commissioner does not believe that recording the size of the sample is burdensome.

472. A comment questioned the need for recording in the laboratory records the date of receipt of a sample by the laboratory, as required by 211.194(a)(1). The comment suggested use of the date of sampling instead. The Commissioner does not agree that recording the date of receipt of a sample by the laboratory is unnecessary. Laboratories commonly log samples showing the date that they are received by the laboratory. Some analyses, such as moisture content of a granulation, may be influenced by the elapsed time between sampling and assay.

It therefore becomes necessary to know both when the sample was drawn and when it was received by the laboratory. The final regulations are revised to clarify that both the date of sampling and the date of receipt for analysis and testing are required.

473. One comment on 211.194(a)(1) questioned the necessity of describing the sample if the other specified information is available. The intent of this requirement is to provide enough of a description to identify the sample properly, such as the name of the drug product and the form of the sample, e.g., granulation, raw material, or powder.

The Commissioner concludes that this is reasonable information to require and, that the requirement reflects current practice.

474. One comment said the meaning of the words "source" and "quantity" in 211.194(a)(1) is not clear. The comment further stated that "quantity" could mean the number of sample containers, which is a reasonable requirement, or it could mean the weight or measure in each sample container, which is not reasonable. The Commissioner rejects the argument that the word "quantity" in the context of 211.194(a)(1) could be interpreted to mean only the number of sample containers with no reference to the amount of sample in each container.

The size of sample containers could range, for example, from a liter container to a container that holds only a few grams. Further, the Commissioner does not believe this requirement to be either unreasonable or burdensome. The Commissioner also concludes that the meaning of the word "source" in 211.194(a)(1) needs clarification. "Source" of the sample is intended to mean the location, e.g., a specific drum number and storage area or in-process phase. The final regulation is revised in this regard.

475. Several comments suggested that the last sentence of 211.194(a)(2) be deleted because the requirement was stated in the second sentence in this paragraph. The Commissioner does not agree with these comments. The last sentence of 211.194(a)(2) requires that testing methods, whether such methods have been developed by the manufacturer or are from official compendia, be verified under actual conditions of use.

The Commissioner does not believe that the requirement in this last sentence is explicitly stated previously.

476. One comment argued that the requirement in 211.194(a)(2) that laboratory records contain a statement of each analytical method used in the analysis of a sample should be limited to assays and should not extend to other tests such as physical tests. The Commissioner does not agree that the requirement should be limited to assays of components of drug products.

Tests or examinations other than assays are an integral part of the history of a drug product, especially in situations where a physical test might be as critical as an assay--for example, in determining particle size, dissolution rate, or tablet hardness. Recognizing, however, that this section as worded in the proposal is somewhat ambiguous in this regard, the Commissioner is rewording the final regulation to reflect that

the requirement applies to all tests, including examinations and assays.

477. Several comments suggested that the words "where appropriate," "where meaningful," or "where required" be added at the end of 211.194(a)(3). One comment reasoned that the size of the sample is not pertinent for many laboratory tests, e.g., melting point, infrared identification, qualitative colorimetric spot tests, and pH. The Commissioner accepts the intent of these suggestions and is revising 211.194(a)(3) accordingly by adding the phrase "where appropriate" in order to provide for test procedures where a nonspecific weight or measure is used.

478. Several comments requested deletion of the requirement in 211.194(a)(4) to include all "graphs, charts, and spectra from laboratory instrumentation" in laboratory records because they are not needed and would create additional files. The Commissioner believes that all graphs, charts, and spectra used to show a product's acceptability must be retained for future reference. These records would be needed to carry out any investigation required under these regulations.

479. Several comments requested deletion of the requirement in 211.194(a)(4) that laboratory records include data on testing of drug product containers and closures. The Commissioner believes that the records generated showing the acceptability or nonacceptability of the containers and closures are as necessary as those for components, in-process materials, or drug products and therefore rejects the request for deletion.

480. Several comments requested 211.194(a) (4) and (5) be revised to take into account calculations and data derived from automatic testing equipment, such as computers. The Commissioner notes that 211.68 already provides for calculations and data derived from automated equipment and

that such provisions need not be restated in every section where they would apply.

481. In considering comments relating to proposed 211.194(a)(6), the Commissioner concludes that those requirements are more appropriately codified as 211.194(b). Specific comments are responded to beginning with paragraph 488 below.

482. Some comments on proposed 211.194(a)(7) (now 211.194(a)(6)) recommended that the phrase "drug product container, closure" be altered to apply only to human drug product containers and closures. The Commissioner finds that recordkeeping should apply to pertinent information regardless of the intended use of the drug product.

483. Several comments on proposed 211.194(a)(7) objected to requiring the laboratory to make a comparison of the test result against an established standard, especially where a standard is not known to the laboratory personnel. Some of these comments suggested alternative wording to clarify this. One comment objected to requiring this statement if the reported result was close to the specification.

The Commissioner believes there must be established standards that all test results are compared against, whether they be precise standards, an acceptable range of values within maximum and minimum values, or the absence or presence of certain attributes. The Commissioner does not understand how respondents would evaluate the significance of test results if no standards for comparison exist. Therefore, this requirement as proposed is retained in the final regulation.

484. Several comments on proposed 211.194(a)(8) (now 211.194(a)(7)) suggested the use of alternative systems of identification instead of a full signature of the person who performs each assay or test. Suggested alternatives were employee numbers or initials. The Commissioner agrees that a

full signature is not needed in this instance and therefore is amending 211.194(a)(7) to allow the use of initials.

485. Several comments suggested that 211.194(a)(8) (proposed as 211.194(a)(9)) be deleted on a variety of grounds--it would be a waste of technical manpower; it would be inflationary; and it is not current practice for the veterinary industry. Other comments suggested provision for a random review or the insertion of the phrase "when such records are audited."

The Commissioner has evaluated all these comments in light of the objective of having independent verification of the laboratory work to insure that the proper procedures were used and followed, that the calculations are correct, and that the record is complete. A review of laboratory records is necessary to insure that the correct test was performed, that the calculations are correct, and that the record is complete. This is not wasteful of resources or unjustifiably costly.

The Commissioner finds it difficult to accept the stated premise that the veterinary drug industry does not review laboratory records to determine whether the proper tests, assays, or examinations have been performed and that the results are valid. It is the Commissioner's belief that drugs for veterinary use, like drugs for human use, must be produced under appropriate control.

The Commissioner rejects the suggested revisions that limit the review to a random basis or to periodic audits. The analytical record for each batch must be reviewed in order to detect whether or not the correct procedure was used, the calculations are correct, and the laboratory record is complete.

486. Some comments suggested that the records reviewed need not always be "original." The Commissioner notes that "original" is used to convey the intent that the records reviewed be those which contain the data used in

conducting tests. The original records give the necessary assurance that complete information is being reviewed. Further, the Commissioner believes it is feasible, and does not believe it is burdensome, to require that the original records be reviewed.

487. One comment suggested that the word "signature" be substituted for the word "endorsement" in 211.194(a)(8). To clarify 211.194(a)(8), it is revised to state that the records shall consist of initials or signature.

488. One comment on proposed 211.194(a)(6) (now 211.194(b)) suggested inclusion of the phrase "or suitable reference to" after the phrase "a full description of." The Commissioner agrees that it is not necessary to describe fully a modification of an established method each time the method is used. The Commissioner has appropriately reworded this requirement in the final regulation to clarify this issue.

489. One comment on proposed 211.194(a)(6) suggested that the word "sample" be substituted for the word "material" because "material" is undefined. The Commissioner believes that the meaning of "material" is clear when considered in the context of this section, now codified as 211.194(b). The term is used broadly to denote any materials, for example components, in-process materials, drug products, containers, or closures, which are tested in consideration of the quality of the drug product.

490. One comment on proposed 211.194(a)(6) (now 211.194(b)) suggested that the word "significant" be inserted before "modification" to preclude the necessity of validating a minor change, such as glassware. The Commissioner rejects this suggestion. If a method, when developed, published, and adopted, describes a procedure to be followed and types of materials to be used in its application, then any deviation from the prescribed procedures or materials may invalidate the results.

491. Comments on 211.194 (c) and (d) (proposed as 211.194(b) and 211.194(c), respectively) recommended substituting the word "adequate" for "complete" or deleting the word "complete" because these sections do not detail the criteria for the content of the records. The Commissioner rejects these recommendations because the word "complete" is intended to require that the records contain all the generated data of all of the tests performed to assure that the laboratory reference standards, reagents, and standard solutions are suitable for use and that periodic calibration of pertinent equipment was accomplished.

The Commissioner believes that it is not feasible to list in detail all the tests or procedures to be performed. 492. Several comments suggested deletion of the phrase "apparatus, gauges, and recording devices," and others recommended deletion of the word "apparatus," in both 211.160(b) and 211.194(d). One comment said this requirement, as stated, could be interpreted by FDA investigators as including beakers, hot plates, and pipette washers.

The Commissioner notes that 211.194(d) cites 211.160(b)(4), which requires the calibration of instruments, apparatus, gauges, and recording devices at suitable intervals. In the case of pipettes, for example, it would not be suitable to calibrate at intervals since under normal conditions of use their capacity does not fluctuate. The Commissioner also recognizes that some equipment and apparatus cannot be calibrated, in which case the requirement obviously does not apply.

493. Comments on 211.194(e) (proposed as 211.194(d)) pointed out that 211.166 only requires stability testing of drug products, not components or in-process materials; therefore, the record retention provisions of 211.194(e) should apply only to stability testing of drug products. The Commissioner agrees that the recordkeeping requirement of 211.194(e) is intended to apply to stability

testing performed in accordance with 211.166, and the final regulation is revised accordingly.

The Commissioner advises, however, that where stability testing of components or in-process materials is conducted, for example, as a part of the testing program to assess the stability characteristics of the drug product under 211.166, the records of such stability testing are appropriately included under 211.194(e).

DISTRIBUTION RECORDS

494. Several comments suggested that 211.196 be revised to provide that information required by this section be readily retrievable.

The Commissioner notes that this is provided for in 211.150(b). There is no need to repeat such a provision in this section.

495. One comment on 211.196 said the lot or control number is not necessary because recalls can be accomplished by contacting every customer. The Commissioner does not believe that reliance on this system of contacting every customer in case of recall is sound. Under such a system recalls could be delayed if customers who received recalled products were not contacted because they were not customers at the time of initiation of the recall.

Conversely, customers who never received the product could be contacted, thus taxing the resources of the firm and FDA. A blanket recall might also cause unneeded patient anxiety and even drug shortages. Additionally, the Commissioner does not believe that the same accountability for each lot is inherent in a system that relies on contacting every customer.

The amount of a recalled product that each customer received may be necessary information if the danger to health is severe

enough to require that each unit of a recalled drug product be accounted for.

496. One comment on 211.196 questioned the necessity for a lot number on distribution records being maintained by suppliers of compressed medical gas. The Commissioner strongly believes that the requirements of this section should apply to compressed medical gas fillers.

Compressed medical gases are potent drug products and, for example, a mixup in labeling of cylinders could constitute a most serious health problem. It could be imperative that every cylinder of a particular lot be accounted for. The Commissioner realizes that usually, compressed medical gases are distributed within a relatively small geographical area and to a limited number of customers, but this is not a sufficient reason to exempt suppliers from the requirements of this section. The requirements of 211.196 should not constitute a major burden on this industry in view of the limited number of customers that are typically serviced by one establishment.

497. One comment on 211.196 questioned the appropriateness of a customer code number on the distribution record in place of the customer's name and address if there is a breakdown of the code. The Commissioner would deem the use of this type of system to be in compliance with the requirements of this section as long as adequate controls are employed to insure the accuracy of the code and legibility on the distribution record.

COMPLAINT FILES

498. Many comments addressed 211.198(a). The comments mostly objected to designation of the quality control unit for reviewing all complaints. The Commissioner has considered the extensive objections and concludes that revisions are necessary to clarify the intended requirements regarding complaint files.

As indicated in the preamble to the February 13, 1976, proposal, the object is to specify more clearly how complaints regarding drug products are to be handled. It is not FDA's intention to restrict or limit review of such complaints to any one unit in the firm's organization, but to assure that the quality control unit is properly involved.

Where there is a complaint involving the possible failure of a drug product to meet any of its specifications, the quality control unit is probably the most appropriate unit to determine whether an investigation under the procedures described in 211.192 is required. To provide manufacturers with as much latitude as possible for efficient review of drug product complaints, the final regulations provide that written procedures for handling complaints include review by the quality control unit where there is a possible failure of a drug product to meet its specifications.

The final regulations also provide that in such instances the quality control unit shall make a determination as to the need for an investigation in accordance with 211.192. This provision allows judgment in determining the extent of the investigation. To safeguard against perfunctory review of complaints, 211.198(b) requires a statement of the rationale for determining that no investigation is necessary and the identity of the person making that determination.

499. The comments regarding the recordkeeping provisions of 211.198(b) objected primarily to the proposed requirement that companies that have more than one establishment maintain a copy of each complaint record at the establishment where the drug product involved was manufactured, processed, or packed (but not necessarily at every establishment where held only).

A number of firms indicated that reports of complaints are currently centralized at one location, which often is the headquarters office. The comments were that duplicate records

required at several locations would be confusing, and it would be difficult to be certain that every such record is complete. The comments also cited increased use of electronic and/or mechanical systems at central locations to store and retrieve data and records.

The Commissioner finds that some revisions in the proposed requirements are justified. He recognizes that many firms with multifacility operations depend on centralized systems to analyze, review, and even investigate complaints involving drug products. Therefore, the final regulations provide that the file designated for written records of drug product complaints may be at a central location provided that the written records are available for inspection.

Where an investigation under 211.192 is actually conducted, 211.180(c) requires that records or copies of records of the investigation be readily available at the establishment where the activities described in the records occurred. This means that a record of an investigation conducted under 211.192 must be maintained at the establishment where conducted, but that other records (e.g., of a medical investigation) regarding the drug product complaint may be maintained at a central location.

The Commissioner believes that the provisions of 211.198 will provide sufficient information regarding complaints about drug products that can be identified as to the point of manufacture. Where no investigation under 211.192 is conducted for a drug product complaint, the final regulations require, as was proposed, that the written complaint record include the reason that no investigation is necessary and the name of the responsible person making such a determination.

Because no investigation under 211.192 will have been conducted, and, in some cases, the point of manufacture cannot be ascertained, the Commissioner finds that the written record or a copy of it may be maintained at the place of

manufacture, if known, or alternatively at a facility where it would be readily available for inspection.

500. Many comments objected to the 2-year retention requirement for records under 211.198. The record retention period is revised in line with other sections.

**XVI. RETURNED AND SALVAGED DRUG PRODUCTS,
RETURNED DRUG PRODUCTS**

501. A number of comments said 211.204 implies that a returned drug product must either be destroyed or reprocessed; an argument was made that reshipment of goods "as is" should not be excluded as a possibility. The Commissioner does not believe that the section as worded excludes the possibility of reshipment "as is."

As it applies to destruction or reprocessing, 211.204 concerns returned drug products that have been held, stored, or shipped, before or during their return, under conditions that cause doubt on their integrity. This section does not prohibit reshipment without reprocessing of a drug product if its integrity was never in doubt, or if initially in doubt, subsequent investigations prove the drug product satisfactory. To preclude the possibility of misinterpretation, however, the Commissioner is revising this section in the final regulation.

502. One comment recommended that reshipment of returned drug products to charitable organizations should be exempt from the requirement in 211.204 for recording quantities or lot numbers. The Commissioner does not believe that shipments of drug products to charitable organizations should be any less controlled than drug products shipped to other categories of consumers.

503. Several comments said bioavailability is merely one facet of drug quality, and there is no need to mention it separately in 211.204. Another comment said mentioning bioavailability is inappropriate for CGMP regulations. The Commissioner finds that bioavailability is only one facet of drug quality and finds that it is unnecessary to mention only one of many facets that could be listed.

504. One comment on 211.204 said the only true measure of bioavailability is in vivo testing and that in vivo

testing of returned goods is neither current practice nor realistic. The Commissioner notes that bioavailability testing is not necessarily a requirement for releasing returned goods.

If conditions were such that doubt was cast on a drug product's bioavailability, then suitable bioavailability testing would be required before the returned product could be released for distribution. Tests for bioavailability other than in vivo testing are recognized by FDA as valid in appropriate cases.

505. Several comments argued that the recordkeeping provisions of 211.204 are unnecessary, redundant, and unduly costly for many operations. The Commissioner does not agree with this position. He does not believe such recordkeeping to be unduly burdensome. This section does not require separate records for returned goods containing all the information required by this section, but rather requires firms to be able to identify which, if any, drug products have been returned and for what reason, and to be able to determine their disposition.

The section would not prevent, for example, the disposition portion of the records on returned goods from being a part of normal distribution records if the lot involved were reshipped. The Commissioner does not agree that the requirements for returned goods are unnecessary. For example, a portion of a lot of drug product may be returned because of unusual shipping conditions and the rest of the lot remain in normal trade channels.

If the returned portion of the lot were destroyed and no record were made, there would be an incomplete record of distribution for the lot. In the case of recall, for example, a part of the lot could not be accounted for. 506. One comment on 211.204 said a record of the lot number and other required information need not be retained in the case of returned goods that are destroyed. The Commissioner rejects this comment.

Accountability could not be accomplished in determining the distribution of a lot of drug product if destroyed products were exempt from this requirement. 507. One comment on 211.204 recommended that time limits be established for destruction or reworking a returned drug product--a maximum 30-day time limit if destruction is the course of action, and 60-days if it is reprocessed. The Commissioner finds no justification for establishing such arbitrary time limits. That processing must not go beyond appropriate limits is adequately covered elsewhere in these regulations.

508. One comment on 211.204 noted that the reason for the return was omitted from the items to be included in the records. The Commissioner believes that the reason for return is of primary importance and should be specifically included in this section. Therefore, the section is revised accordingly in the final regulations.

DRUG PRODUCT SALVAGING

The drug product salvaging provisions of these regulations were proposed on two separate occasions--in the FEDERAL REGISTER of January 16, 1975 and February 13, 1976. The comments discussed here include those received after both proposals were published. 509.

One comment said 211.208 could be interpreted as applying also to in-process materials unless further specified. It suggested that the title of the heading be changed to "Packaged Drug Product Salvaging." The Commissioner finds there is no suggestion that this section applies to in-process materials. The section clearly refers to drug products, and that term is defined in 210.3. The control of in-process materials, also defined in 210.3(b), is covered elsewhere in Part 211. 510.

One comment argued that 211.208 is contradictory in that it prohibits salvaging and return of drug products to the

marketplace, and then permits such procedures. The Commissioner disagrees with this comment. The section prohibits the salvaging of drug products and/or return to the marketplace when the drug products have been exposed to improper storage conditions.

The purpose of this section is to provide for an appropriate procedure for determining the suitability of salvaging drug products that may have been exposed to such conditions. The Commissioner believes that this section is adequately worded to convey its meaning.

511. Another comment recommended that the wording of 211.208 be changed to allow manufacturers to determine what testing accurately reflects the condition of the product. The Commissioner rejects this comment. The requirements of this section are the minimum procedures necessary to assure the safety and quality of drug products that may have been exposed to improper storage conditions.

512. A comment said it is unclear when 211.208 applies and when 211.204, "Returned Drug Products" is applicable. The applicability of these sections depends on the history of the drug product. Section 211.204 is revised to require that the reason for return be included in the records pertaining to the returned drug. If the drug product is being returned because of possible exposure to improper conditions, the drug product salvaging requirements of 211.208 must also be applied. The Commissioner believes that both sections clearly state their intent.

513. One comment said the phrase "evidence that the product meets all applicable standards of identity, strength, quality, and purity" should be deleted throughout 211.208 because it is unnecessarily detailed and restrictive. The Commissioner does not understand how the requirement that a drug product meets all applicable standards of identity,

strength, quality, and purity could reasonably be considered either too detailed or too restrictive.

Anything less would not assure the quality and safety of the drug product or that the product was not adulterated under the act. Therefore, the comment is rejected.

514. A number of comments on 211.208 expressed concern that manufacturers and/or distributors do not have absolute control over a drug once it leaves their premises, and without evidence of proper control, drugs could not be returned under the proposed regulations, even in the normal course of a firm's business. They cited examples such as returning overstocked items, drugs which were ordered or distributed in error, seasonal items, recertified antibiotics, or drugs requiring relabeling.

The Commissioner finds that the CGMP regulations do not prohibit drug products; being returned. The regulations clearly allow redistribution of returned drug products that meet applicable standards of safety, identity, strength, quality, and purity. If there is no question whether the drug products have been properly stored after leaving the manufacturer's control, the testing requirements of 211.208 do not apply.

515. Three comments concerned the interpretation of "prolonged storage" in 211.208. One comment recommended that this term be deleted; another recommended that it be revised to specify a period of time. One comment assumed that a 5-year maximum is preferred by FDA and could be a basis for defining "prolonged storage." The Commissioner finds that, in view of the requirements regarding expiration dating of drug products, the proposed reference to prolonged storage in 211.208 is unnecessary.

The Commissioner concludes that this section should be further revised for simplicity, by referring to "improper storage

conditions" rather than "improper storage or abnormal environmental conditions."

516. One comment on 211.208 recommended that organoleptic examinations be considered acceptable as evidence, provided such a determination is made by a pharmacist or chemist having 1 year's experience in the field. Organoleptic examinations alone would never be enough to insure that a drug has maintained its strength, purity, and quality after it has been in a situation where it may have been exposed to improper storage conditions. Therefore, this comment cannot be accepted.

517. One comment recommended that 211.208 provide for reclaiming of active ingredients from drug products that have been salvaged. The Commissioner finds that drug products that have been subjected to improper storage conditions should not be salvaged because of the resulting questionable integrity of the drug product. Therefore, such drug products are clearly not suitable for reprocessing, including reclaiming of active ingredients.

However, where salvaging is permissible under the provisions of 211.208, any appropriate reprocessing is allowed. The Commissioner believes the regulations are clear in this regard.

XVII. CGMP FOR CERTAIN OTHER DRUG PRODUCTS

518. No comments or objections addressed proposed revocation of 229.25. Section 229.25 is the only section contained in Part 229 (21 CFR Part 229), and the Commissioner sees no immediate need for retaining that part as currently used. Therefore, the entire Part 229 is revoked in these final regulations and reserved for future use.

The Commissioner has carefully considered the environmental effects of the proposed regulation and, because the proposed action will not significantly affect the quality of the human environment, has concluded that an environmental impact statement is not required. A copy of the environmental impact assessment is on file with the Hearing Clerk, Food and Drug Administration.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 501, 502, 505, 506, 507, 510, 512, 701, 52 Stat. 1049-1053 as amended, 1055-1056 as amended, 59 Stat. 463 as amended, 76 Stat. 794 as amended, 82 Stat. 343-351 (21 U.S.C. 351, 352, 355, 356, 357, 360, 360b, 371)) and the Drug Listing Act of 1972 (Pub. L. 92-387; 86 Stat. 559-562) and under authority delegated to the Commissioner (21 CFR 5.1), Chapter I of Title 21 of the Code of Federal Regulations is amended as follows: