Tab B

Federal Register

Thursday,
April 8, 2004

Part IV

Department of Health and Human Services

Food and Drug Administration

21 CFR Parts 206, 250, 314, 600, and 601
Supplements and Other Changes to an Approved Application; Final Rule
Guidance for Industry on Changes to an Approved NDA or ANDA; Availability; Notice

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 206, 250, 314, 600, and 601

[Docket No. 1999N-0193]

RIN 0910-AB61

Supplements and Other Changes to an Approved Application

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its regulations on supplements and other changes to an approved application to implement the manufacturing changes provision of the Food and Drug Administration Modernization Act of 1997 (the Modernization Act). The final rule requires manufacturers to assess the effects of manufacturing changes on the identity, strength, quality, purity, and potency of a drug or biological product as those factors relate to the safety or effectiveness of the product. The final rule sets forth requirements for changes requiring supplement submission and approval before the distribution of the product made using the change, changes requiring supplement submission at least 30 days prior to the distribution of the product, changes requiring supplement submission at the time of distribution, and changes to be described in an annual report.

DATES: This rule is effective June 22, 2004.

FOR FURTHER INFORMATION CONTACT: David J. Cummings, Center for Drug Evaluation and Research (HFD-357), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-5187, or Robert A. Yetter, Center for Biologics Evaluation and Research (HFM-10), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852, 301-827-0373.

SUPPLEMENTARY INFORMATION:

I. Background

Section 116 of the Modernization Act (Public Law 105-115) amended the Federal Food, Drug, and Cosmetic Act (the act) by adding section 506A (21 U.S.C. 356a). That section describes requirements and procedures for making and reporting manufacturing changes to approved new drug and abbreviated new drug applications, to new and abbreviated animal drug applications, and to license applications for biological products under section 351 of the Public Health Service (PHS) Act (the PHS act). Section 506A of the act revises current procedures for approving manufacturing changes. Major manufacturing changes, as defined in section 506A of the act, are of a type determined by the Secretary of Health and Human Services (the Secretary) to have a substantial potential to adversely affect the identity, strength, quality, purity, and potency as they may relate to the safety and effectiveness of a drug. Such changes require prior approval of a supplemental application. Section 506A of the act also states that the Secretary may require submission of a supplemental application for drugs made with manufacturing changes that are not major and may establish categories of manufacturing changes for which a supplemental application is required. In such a case, the applicant may begin distribution of a drug 30 days after FDA has received a supplemental application unless the agency notifies the applicant within the 30-day period that prior approval of the application is required. Under the statute, FDA may also designate a category of manufacturing changes that permit the applicant to begin distributing a drug made with such changes upon receipt by the agency of a supplemental application for the change. Finally, FDA may also authorize applicants to distribute drugs manufactured with a change without submitting a supplemental application. The law provides that FDA may establish categories of manufacturing changes that may be made without submitting a supplemental application.

A. Development of the Regulation

In the **Federal Register** of June 28, 1999 (64 FR 34608), FDA published a proposed rule to implement section 506A of the act for human new drug applications (NDAs) and abbreviated new drug applications (ANDAs), as well as for licensed biological products (the June 1999 proposal). In that same issue of the **Federal Register** (64 FR 34660), FDA announced the availability of a draft guidance for industry entitled "Changes to an Approved NDA or ANDA." This guidance was intended to assist applicants in determining how they should report changes to an approved NDA or ANDA under section 506A of the act as well as under the proposed revisions to the human drug regulations pertaining to supplements and other changes to an approved application. In the **Federal Register** of November 23, 1999 (64 FR 65716), FDA announced the availability of a guidance to assist applicants in determining how they should report changes to an approved NDA or ANDA under section 506A of the act, pending finalization of the June 1999 proposal. FDA has revised the guidance to conform to this final rule and is announcing the availability of the guidance elsewhere in this issue of the **Federal Register**.

B. A Risk-Based Approach

The publication of this final rule is an important step in the process of adopting a risk-based approach to the regulation of pharmaceuticals. In the 1990s, FDA sponsored research at the University of Maryland and other universities on the types of chemistry and manufacturing changes to immediate release solid oral drug products that could affect drug performance (i.e., identity, strength, quality, purity, and potency) and, therefore, safety and effectiveness. Using that research, FDA's Center for Drug Evaluation and Research (CDER) began to develop a risk-based approach to the implementation of manufacturing changes. The approach provided for a continued high level of scrutiny by FDA of changes that were most likely to affect the performance of a drug and decreased scrutiny of changes that were not likely to affect the performance of a drug.

The risk-based approach was first explained in a series of guidance documents (the Scale-up and Postapproval Changes (SUPAC) guidances) that reduced the regulatory burden of obtaining FDA authorization to make certain changes. The work continued in regulations issued by the Center for Biologics Evaluation and Research (CBER) in 1997 (21 CFR 601.12). In November 1997, this risk-based approach was codified in section 116 of the Modernization Act.

This final rule implements section 116 of the Modernization Act by incorporating the statutory standards for characterizing proposed changes as having substantial, moderate, or minimal potential to adversely affect the identity, strength, quality, purity, and potency of a drug as they may relate to its safety and effectiveness and determining submission requirements based on the potential risks associated with the changes. For changes with a substantial potential to affect the designated characteristics of a drug, FDA must review and approve a supplement that contains information showing that the proposed change will not adversely affect the drug's characteristics (i.e., information developed by the holder of the application to validate the effect of the proposed change) before distribution of the product made using the change.

It was anticipated when section 116 of the Modernization Act was written that the science of manufacturing would evolve over time and affect whether changes would be considered major or nonmajor. To accommodate future technological advancements, section 116 of the Modernization Act and this final implementing regulation both provide that FDA may, by regulation or guidance, change the designation of a particular category of change from major to nonmajor or vice versa. This concept of an evolving risk-based approach to manufacturing changes also is consistent with the agency's Good Manufacturing Practices Initiative ("Pharmaceutical cGMPs for the 21st Century," *www.fda.gov/cder/gmp/index.htm*). The goals of that initiative, launched in August 2002, include:

- Ensuring that state-of-the-art pharmaceutical science is utilized in the regulatory review and inspection policies;
- Encouraging the adoption of new technological advances in high quality and efficient manufacturing by the pharmaceutical industry;
- Assessing the applicable current good manufacturing practice (CGMP) requirements relative to the best quality management practices;
- Strengthening public health protection by implementing risk-based approaches that focus both industry and FDA attention on critical areas for improving product safety and quality; and
- Enhancing the consistency and coordination of FDA's drug quality oversight activities.

Specifically, one of the efforts of the CGMP initiative is to facilitate continuous improvement and innovation in manufacturing by allowing manufacturers to make certain types of changes in their processes without prior FDA approval. This rule, in keeping with that initiative, provides for a mechanism of continuous improvement through the guidance process (21 CFR 10.115) that may provide for less burdensome documentation of certain changes as manufacturing processes and pharmaceutical science develop.

II. Highlights of Revisions to the Proposed Rule

A. Definitions

FDA has revised the proposed definition of "specification" by changing the phrase "other components including container closure systems and in-process materials" to "components, in-process materials, container closure systems, and other materials used in the production of a drug substance or drug product." FDA made this change for consistency with other regulations. FDA proposed a definition for the term "validate the effects of the change." In the final rule, the agency has changed the word "validate" to "assess" and provides a definition for the term "assess the effects of the change."

B. Changes to an Approved Application

The proposal required that the holder of an approved application validate the effects of manufacturing changes on the identity, strength, quality, purity, and potency of the drug as these factors may relate to the safety or effectiveness of the drug. FDA has revised this provision to require that the holder of an approved application assess the effects of manufacturing changes. FDA has deleted the phrase "on the identity, strength, quality, purity, and potency of the drug product as these factors may relate to the safety or effectiveness of the drug product" because this information is already included in the definition of the term "assess the effects of the change."

Previously, § 314.70(c) (21 CFR 314.70(c)) stated that the applicant who submits a changes-being-effected supplement to FDA must promptly revise all promotional labeling and advertising to make it consistent with any change in the labeling. The proposal retained this provision and FDA stated in the preamble that the requirement would apply equally to all labeling changes. FDA has revised this provision to limit the requirement to those labeling changes submitted in supplemental applications and not to those in annual reports.

The proposal required the applicant to include in a cover letter a list of all changes contained in the supplement or annual report. FDA has clarified that the requirement to include the list of changes in a cover letter applies only to changes contained in a supplement; the information is already submitted in an annual report.

C. Changes Requiring Supplement Submission and Approval Prior to Distribution of the Product Made Using the Change (Major Changes)

FDA has limited the requirement to include only those changes to a drug product container closure system that involve changes in the type or composition of a packaging component. FDA intends to provide additional guidance on container closure systems changes that will be considered moderate changes or changes that can be reported in an annual report.

FDA proposed to require that a reference list of relevant standard operating procedures (SOPs) be contained in all supplements submitted under this section. FDA has revised this provision to specify that a reference list of relevant SOPs must be submitted for changes to a natural product, a recombinant deoxyribonucleic acid (DNA)-derived protein/polypeptide product, or a complex or conjugate of a drug substance with a monoclonal antibody, and for changes to the sterilization process and test methodologies related to sterilization process validation.

D. Changes Requiring Supplement Submission at Least 30 Days Prior to Distribution of the Drug Product Made Using the Change (Moderate Changes)

FDA has revised the June 1999 proposal to clarify that the requirement to submit 12 copies of finished product labeling applies to supplements for changes that may be implemented 30 days after FDA receives the supplement.

FDA has clarified that the changes in the container closure system submitted in supplements under these moderate changes provisions do not include the changes described under the provisions requiring prior approval or the changes submitted in an annual report.

FDA has revised the changes solely affecting a natural protein product, a recombinant DNA-derived protein/polypeptide product, or a complex or conjugate of a drug with a monoclonal antibody to specify the use of "different equipment" instead of "new or different equipment" for changes in production scale, and equipment of "a different design" instead of "similar but not identical design and operating principle" for the replacement of equipment.

FDA is also adding to the moderate changes provisions a change in the relaxation of an acceptance criterion or deletion of a test to comply with an official compendium that is consistent with FDA statutory and regulatory requirements. FDA is not requiring that a prior approval supplement be submitted for this type of change because the change has been reviewed by the United States Pharmacopeia (USP), and FDA and the public have had an opportunity to review, in general, the change through the USP process. However, because FDA will not have reviewed such a change in the context of each individual application affected by the change, a changes-being-effected-in-30-days supplement will still be required.

FDA has revised the proposal to clarify that the applicant may not

distribute the drug product until the supplement for a change under this provision has been amended to provide missing information that has been requested by FDA.

E. Changes That May Be Implemented When FDA Receives a Supplement (Moderate Changes)

FDA has clarified that labeling changes that normally require a prior approval supplement may, at the agency's request, be implemented when FDA receives a supplement.

F. Changes To Be Described in the Next Annual Report

FDA has revised the June 1999 proposal to state that any change made to comply with an official compendium that is consistent with FDA statutory and regulatory requirements may be submitted in the next annual report, except a change involving the relaxation of an acceptance criterion or deletion of a test to comply with an official compendium.

FDA has revised the June 1999 proposal to clarify that the majority of changes concerning replacement of equipment with equipment of the same design and operating principles may be submitted in an annual report. However, there are certain equipment changes identified in this rule that require submission in a changes-being-effected-in-30-days supplement or a changes-being-effected supplement.

FDA has revised the June 1999 proposal to clarify that certain changes made to the container closure systems for sterile drug products may be submitted in annual reports, as may certain changes for nonsterile drug product container closure systems. The changes are those based on a showing of equivalency under an approved or official compendium protocol.

FDA has revised the June 1999 proposal to clarify that an extension of an expiration dating period that can be reported in an annual report can be based on production batches instead of full production batches. FDA considers a production batch to be one made at production scale using production equipment in a production facility as specified in the application. Production scale does not necessarily mean the largest batch size produced, but a batch of a size or within a batch size range that has been approved in the application.

FDA has deleted the requirement that an annual report contain a list of all products involved in the changes. FDA has also clarified that an annual report must include the date each change was implemented instead of the date each change was made. FDA considers "the date each change was implemented" to be the date that the condition established in the approved application is changed, not when the product made with the change is distributed. FDA has also revised the June 1999 proposal to clarify when validation protocols and SOPs must be included in an annual report submission.

G. Other Information

FDA has revised the June 1999 proposal to clarify that a protocol must be submitted as a prior approval supplement if the protocol was not already included in an approved application or when changing an approved protocol. In the June 1999 proposal, FDA used the terms "drug," "drug product," "drug substance," and "product." The agency has standardized the terminology throughout the final rule and used the terms "drug product," "drug substance," and/or "product" as appropriate. In addition, the agency has made minor edits to the final rule in response to former President Clinton's June 1, 1998, memo on plain language in Government writing.

III. Responses to Comments on the June 1999 Proposal

FDA received comments on most aspects of the June 1999 proposal from more than 30 pharmaceutical companies, pharmaceutical industry associations, and other interested persons. The comments and the agency's responses follow.

A. General Comments

(Comment 1) Many comments said the June 1999 proposal does not meet the intent of Congress when establishing section 506A of the act. The comments said that Congress expected the following: (1) Significant changes in FDA's past practices on manufacturing changes; (2) substantial improvement in the management of technical supplements for manufacturing changes; (3) regulatory relief without compromising quality, safety, or efficacy of drugs; (4) appropriate action on the marketing of regulated products in a manner that does not unduly impede innovation or product availability; (5) reduction in reporting and regulatory requirements; and (6) a small number of major manufacturing changes that require prior approval, but that most changes would require a less burdensome means of reporting than has been required in the past. Several comments said the June 1999 proposal generates new requirements for making regulatory submissions, adds new categories for making those submissions, and increases the documentation burden on industry. One comment also noted that the SUPAC guidances[1] would not fulfill the Congressional intent because they were published before the Modernization Act.

FDA believes that these regulations are consistent with the intent of Congress and that the regulatory requirements and reporting categories are consistent with section 506A of the act. Section 506A of the act provides FDA with considerable flexibility to determine the information and filing mechanism required for the agency to assess the effect of manufacturing changes in the safety and effectiveness of the product. There is a corresponding need to retain such flexibility in the proposed regulations implementing section 506A of the act to ensure that the least burdensome means for reporting changes are available. FDA believes that such flexibility will allow it to be responsive to increasing knowledge of and experience with certain types of changes and help ensure the efficacy and safety of the products involved. For example, a change that may currently be considered to have a substantial potential to have an adverse effect on the safety or effectiveness of the product may, at a later date, based on new information or advances in technology, be determined to have a lesser potential to have such an adverse effect. Conversely, a change originally considered to have a minimal or moderate potential to have an adverse effect on the safety or effectiveness of the product may later, as a result of new information, be found to have an increased, substantial potential to adversely effect the product.

The agency believes it can more readily respond to knowledge gained from manufacturing experience, further research and data collection, and advances in technology by issuing regulations that set out broad, general categories of manufacturing changes and by using guidance documents to provide FDA's current thinking on the specific changes that fall into those general categories. The regulations provide for a new approach to regulating postapproval manufacturing changes. The approach is based on the potential for a change to adversely affect the identity, strength, quality, purity, or potency of drug products as these factors relate to the safety and effectiveness of the product. The

[1] As explained in the June 1999 proposal, FDA developed the SUPAC guidances to ease preapproval requirements by categorizing certain manufacturing changes according to whether they had a minor, moderate, or major potential to affect product quality and performance.

regulations and companion guidance "Changes to an Approved NDA or ANDA" will provide significant regulatory relief by allowing postapproval manufacturing changes to be implemented more rapidly, while still ensuring the identity, strength, quality, purity, and potency of drug products.

The regulation reduces the overall number of supplements requiring FDA approval prior to product distribution. In addition, many changes that are currently reported in supplements would be reported in annual reports. The regulation will not increase the number of annual reports but will allow applicants to include in an annual report information currently required to be reported to the agency in a supplemental application. The number of manufacturing changes currently reported in supplements that will be reported in annual reports is approximately 1,283.

For example, under the previous regulations, all manufacturing site changes for drug products required prior approval. Now only a few types of drug product manufacturing site changes must be submitted in a prior approval supplement. The majority can be submitted in a changes-being-effected-in-30-days supplement or in an annual report. Moreover, FDA further reduced many reporting requirements from the levels recommended in previous FDA guidances. For example, the SUPAC guidances recommended notification in an annual report when moving production operations between buildings at the same manufacturing site. Now, generally no notification is required for such changes affecting drug products that were covered under the following SUPAC guidances: (1) "Immediate-Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation" (SUPAC–IR); (2) "Modified Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation" (SUPAC–MR); and (3) "Nonsterile Semisolid Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Release Testing, and In Vivo Bioequivalence" (SUPAC–SS).

FDA believes that the approach to postapproval changes embodied in the SUPAC guidances is consistent with section 506A of the act. However, certain aspects of these documents need to be updated to be consistent with specific requirements included in the act. For example, the new reporting category for changes-being-effected-in-30-days supplements needs to be incorporated. FDA intends to update these guidances in the near future.

(Comment 2) Several comments said that FDA should adopt a "decision tree" or "key questions" approach in implementing section 506A of the act. The comments contend that this approach would allow a new approach to manufacturing changes that bases the regulatory reporting requirements on the results of scientific comparison of pre- and post-change material rather than allowing the reporting category to be determined by the potential for a change to have an adverse effect. The decision tree would focus on answering the key questions rather than exhaustive categorization of potential types of changes. One comment provided examples of decision trees for consideration.

FDA agrees that decision trees are a viable approach to postapproval manufacturing changes. However, a decision tree must consider the potential for a change to have an adverse effect to be consistent with section 506A of the act. The act bases the reporting category for a change on the potential for that change to have an adverse effect, not on the outcome of assessment studies. In some cases, based on the potential for an adverse effect, the act would require FDA to review a change prior to distribution of the drug product with the change, even if the applicant concludes that its studies and data demonstrate that the change has no significant adverse effect. FDA must evaluate whether the studies performed by the applicant were sufficient to assess the effect of the change and whether the data support the applicant's claim that the change has not adversely affected the identity, strength, quality, purity, and potency of the drug product as they may relate to the safety or effectiveness of a drug product. For example, an applicant may decide to develop an in vivo/in vitro correlation (IVIVC) for an extended release oral dosage form (see CDER's guidance entitled "Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In vitro/In vivo Correlations" (September 1997)). If an IVIVC is established, the dissolution test will be used by the applicant as a surrogate for in vivo bioequivalence when it is necessary to document bioequivalence for postapproval changes. Establishing an IVIVC has a significant potential to affect the identity, strength, quality, purity, and potency of the drug product as they may relate to safety and effectiveness of the drug product, and requires a prior approval supplement. The applicant, based on its evaluation of the data, may believe that an IVIVC has been established but the agency, after evaluation of the applicant's data, may not concur. If the applicant decided that a prior approval supplement was not necessary based on its conclusions that an IVIVC has been established and implemented the change without waiting for the agency's concurrence, a drug product that is not bioequivalent could be distributed to the public.

FDA regulates a wide range of products, and a decision tree should address the fact that the potential for adverse effect will vary depending on factors such as the dosage form and route of administration. For example, in general, packaging changes that involve parenteral drug products are viewed by FDA to have a higher potential to have an adverse effect on the quality of the drug product as it relates to the safety and efficacy of the drug product than a packaging change for a solid oral dosage form product. Leachables from the packaging into parenteral drug products are more likely to occur than for a solid oral dosage form, and if leaching occurs, there is a higher potential for adverse reactions because of the route of administration. A safety determination by FDA must be made before the change is implemented. An applicant wishing to rely on a decision tree can submit the decision tree using an appropriate mechanism, such as submission of a comparability protocol containing a decision tree, and FDA will evaluate the decision tree for consistency with section 506A of the act.

(Comment 3) Another comment said that the proposal consisted of heightened reporting requirements for changes in packaging materials for sterile liquid dosage forms.

Previously, under § 314.70(b), changes in packaging for sterile liquid dosage forms routinely required prior approval by FDA before they could be implemented. The final rule, at § 314.70(b)(2)(iii), still emphasizes the importance, from the safety perspective, of ensuring the sterility of drug products by requiring that changes that may affect drug product sterility assurance be reported in a prior approval supplement. However, the guidance "Changes to an Approved NDA or ANDA," announced elsewhere in this issue of the **Federal Register**, includes certain changes in the packaging of these products that can be implemented by means other than prior approval supplements. This action has reduced, rather than heightened, the regulatory

burden relating to the packaging of sterile liquid dosage forms. FDA has included these changes in the guidance because, as stated in the proposal, the agency believes it can more readily respond to knowledge gained from manufacturing experience, further research and data collection, and advances in technology by issuing regulations that set out broad, general categories of manufacturing changes and by using guidance documents to provide FDA's current thinking on the specific changes that fall into those general categories (64 FR 34608 at 34610). Section 506A of the act explicitly provides FDA the authority to use guidance documents to determine the type of changes that do or do not have a substantial potential to adversely affect the safety or effectiveness of the drug product. As discussed previously in this document, the use of guidance documents will allow FDA to more easily and quickly modify and update important information. Guidance documents will be developed according to the procedures set out in FDA's good guidance practices (see the **Federal Register** of September 19, 2000 (65 FR 56468), and 21 CFR 10.115).

(Comment 4) Another comment requested that FDA specifically address in the final rule and/or guidance or in separate guidance how a change in the device aspect of a drug-device combination product is to be reported in applications. The comment said that when establishing rules for reporting changes in packaging and packaging components, FDA should not simply apply the rules for changes to drugs and biologics to the device-like aspects of combination products. Rather, the comment said, FDA should consider how the equivalent change is managed for the analogous medical device and apply that approach.

CDER and CBER work cooperatively with the Center for Devices and Radiological Health (CDRH) in the review of drug-device combinations. Determinations as to which regulations apply to a given combination product are product and application specific. Sponsors of combination products should consult with the Center that provided the approval of their application and with the Office of Combination Products to determine what requirements are applicable to the changes they wish to make to their product.

(Comment 5) Several comments said that the proposal put an overwhelming emphasis on postapproval changes for drug products and little on drug substances. The comments identified the following concerns: (1) The proposal is written entirely from the perspective of NDA and ANDA applicants and includes nothing for Drug Master File (DMF) holders; (2) a reporting classification system depending on the potential of a change to have an impact may usually work in the drug product area but is less apt to work for the drug substance, where the actual change may only be gauged by the data obtained when the change is made; and (3) the processes used in drug product and drug substance manufacturing differ greatly, making it difficult to determine how the changes outlined for drug products apply to drug substances. Several comments said that a separate document addressing changes relating to drug substances should be prepared.

The regulations emphasize changes in drug products and are written for NDA and ANDA applicants because the regulations describe the procedures for notifying FDA about changes in conditions established in an approved drug product application. Changes in a drug substance are only one of many types of changes that may occur in a drug product application. FDA has provided specific recommendations on drug substance changes in the guidance entitled "Changes to an Approved NDA or ANDA." In the **Federal Register** of February 16, 2001 (66 FR 10699), the agency announced a guidance that focuses specifically on postapproval manufacturing changes for certain drug substances entitled "BACPAC I: Intermediates in Drug Substance Synthesis, Bulk Actives Postapproval Changes: Chemistry, Manufacturing, and Controls Documentation" (the BACPAC I guidance). FDA believes that the BACPAC I guidance addresses the concerns expressed in the comments.

(Comment 6) Several comments reiterated comments previously provided to the agency on the guidances entitled "BACPAC I" and "Changes to an Approved NDA or ANDA," and asked FDA to consider these comments in finalizing the proposed regulation.

FDA has considered and addressed these resubmitted comments in this document to the extent that they were applicable to the proposed regulation.

(Comment 7) Another comment said that FDA should provide for realistic and workable filing mechanisms and requirements with regard to changes in the manufacturing of drug substances where the information is included in DMFs.

The regulations and companion guidance entitled "Changes to an Approved NDA or ANDA" provide recommendations on reporting changes in the conditions established in an approved application, including changes in drug substance covered by DMFs. Issues relating to DMFs and how these are used in the application review process are outside the scope of this rulemaking.

(Comment 8) One comment stated that the rule should clearly address how changes in the manufacture of pharmaceutical packaging and pharmaceutical packaging components are to be handled. The comment said that the current regulation and the proposal and guidance address this issue incompletely, and frequently packaging and packaging component manufacturers are left to try to interpret the regulation as it applies to packaging.

FDA has clarified the requirements for packaging components in the final regulations as a result of the public comments and has included information on this topic in the guidance "Changes to an Approved NDA or ANDA."

(Comment 9) Several comments said that the use of broad and vague terms (e.g., any change, may impact) should be minimized. The comments said that such terms lend themselves to different interpretations, are likely to cause confusion and inconsistent application, and are likely to result in more burdensome reporting requirements for changes that would be more appropriately categorized as moderate and/or minor changes. One comment said that FDA should revise these terms, and suggested adding the modifier "significant" or "significantly" in several instances to sharpen the intended meaning. The comment said that since the term "significant" is itself undefined, it suggests that, in this context, "significant" means "likely to adversely affect the identity, strength, quality, purity or potency of the related product."

FDA agrees that the use of broad and vague terms should be minimized and has clarified the regulation, as appropriate, in response to comments received on the use of such terms as "any change" and "may impact," and those comments suggesting adding the term "significant."

(Comment 10) One comment asked whether the final regulations will contain references to appropriate guidance documents.

The final regulations do not reference specific guidance documents. FDA continues to update and develop guidances to address particular regulatory and scientific issues, and any references included in a regulation may quickly become outdated. Guidances that provide FDA's current thinking on specific topics can be located on the Internet at *http://www.fda.gov/cder/*

guidance/index.htm and *http://www.fda.gov/cber/guidelines.htm.*

(Comment 11) One comment said that although the proposal applies only to human drugs and biologics, the Center for Veterinary Medicine (CVM) may be preparing a similar proposal and may be compelled to apply most if not all of the principles described in the proposed rule. The comment said that the animal drug industry is very pleased with the successful 1996 CVM initiative, "Alternate Administrative Process for the Implementation and Submission of Supplemental Chemistry, Manufacturing and Control Changes (AAP)." The comment said that its support of the Modernization Act was given based on the legal interpretation that the Modernization Act did not preclude the continuation of the AAP program. The comment said that the AAP program succinctly provides a process for determining minor supplemental chemistry, manufacturing, and control changes that are reported on a biennial basis. The comment continues to strongly support the concepts embodied in the AAP and is concerned that implementation of the proposed rule would be more burdensome, on both FDA and industry, than the AAP. The comment said that CVM and Animal Health Institute (AHI) member companies have had 3 years of successful implementation of this program and believe that the proposed rule, if applied to animal drugs, would be a major step backwards.

Comments relating to the AAP are outside the scope of this rulemaking and should be directed to the proposed rule for veterinary drug products entitled "Supplements and Other Changes to Approved New Animal Drug Applications" (published in the **Federal Register** of October 1, 1999 (64 FR 53281)) (the October 1999 proposal).

B. Definitions

FDA proposed to amend the definitions sections of the regulations on applications for FDA approval to market a new drug (§ 314.3 (21 CFR 314.3)) and a biological product (§ 600.3 (21 CFR 600.3)) by adding definitions for "specification" and "validate the effects of the change." Proposed §§ 314.3(b) and 600.3(hh) defined "specification" as the quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, and other components including container closure systems, and in-process materials. The term "acceptance criteria" refers to numerical limits, ranges, or other criteria for the tests described.

FDA has revised the proposed definition of specification to make the use of the term "component" consistent with the definition of "component" at § 210.3 (21 CFR 210.3). FDA has revised the definition as follows:

Specification means the quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, components, in-process materials, container closure systems, and other materials used in the production of a drug substance or drug product. For the purpose of this definition, *acceptance criteria* means numerical limits, ranges, or other criteria for the tests described.

FDA has made the same changes to proposed § 600.3(hh) (new § 600.3(jj)) and clarified the definition of specification for biological products by replacing the phrase "drug substances, drug products" with "products." The term "products" is defined in § 600.3(g).

(Comment 12) Several comments stated that "intermediates, raw materials, reagents, and other components including container closure systems, and in-process materials" should be deleted from the definition of specification, and changes for these materials should be handled separately from the final rule and final guidance. The comments said that the definition is not consistent with the International Conference on Harmonisation (ICH) guidance on specifications entitled "Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances" (ICH Q6A), which includes only drug substance and drug product. The comments said that to include items beyond the drug substance and drug product represents a level of complexity that would be better dealt with in guidances that can adequately evaluate the significance of changes to specific items.

FDA declines to revise the definition as requested. Section 505 of the act (21 U.S.C. 355) requires that a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of a drug be provided in an application. The regulations at § 314.50(d)(1) (21 CFR 314.50(d)(1)) require that an application include specifications as are necessary to ensure the identity, strength, quality, purity, and potency of the drug substance and drug product. Moreover, the regulation at § 314.50(d)(1)(ii)(a) specifically requires that specifications be provided for each component. It identifies specifications for container closures systems as an example of a specification needed to ensure the identity, strength, quality, purity, and potency of the drug product. For biologics, an applicant must submit a full description of manufacturing methods (§ 601.2 (21 CFR 601.2)). Intermediates, raw materials, reagents, container closure systems, in-process materials and other materials that are used in the manufacture of drug substances, drug products, and biologics are considered part of the manufacturing method and can have a direct effect on the identity, strength, quality, purity, and potency of the drug substance, drug product, or biologic. While the extent of a specification (e.g., number or type of tests, strictness of acceptance criteria) for these materials may vary depending on their use in a given manufacturing process, FDA has required specifications for these materials to be included in applications as part of the description of the manufacturing method and will continue to do so.

The ICH Q6A guidance and the ICH guidance on specifications entitled "Test Procedures and Acceptance Criteria for Biotechnology/Biological Products" (ICH Q6B) are limited in scope. For example, ICH Q6A specifically excludes fermentation products. Interpreting the limitations of the ICH guidances to mean that specifications are not required for fermentation products or other materials outside the scope of ICH Q6A or ICH Q6B would be incorrect.

FDA requires specifications for intermediates, raw materials, reagents, container closure systems, in-process materials, and other materials used in the manufacturing process to be included in the application and, therefore, has included these materials in the definition of specification. Any changes in a specification, except editorial, must be reported to FDA and applicants need guidance on how to implement these changes. FDA declines deferring recommendations on these changes to a later guidance and has provided guidance on the recommended reporting categories for changes in specifications in FDA's guidances entitled "Changes to an Approved NDA or ANDA" and "Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products" (July 1997).

(Comment 13) One comment said that the term "specifications and test procedures" was used in part 314 (21 CFR part 314) in the past, but the proposal replaced this with the term "specification," which is intended to mean both tests and specifications. The comment said that using one word to represent several things is confusing

and recommended retaining the previous terminology.

FDA declines to revise the use of the term "specification" as requested. In the past, "specification" as used in part 314 meant numerical limits, ranges, or other criteria for a test. In developing the ICH Q6A and ICH Q6B guidances, FDA agreed to define specification differently. A specification, as defined in ICH Q6A and ICH Q6B, includes tests, analytical procedures, and acceptance criteria. FDA has used the ICH Q6A and ICH Q6B terminology in this rule to promote consistency with the ICH documents.

(Comment 14) One comment identified various types of specification changes and recommended how these should be categorized and reported.

FDA declines to expand the discussion of specification changes in the regulation. As stated in the June 1999 proposal, the agency believes it can more readily respond to knowledge gained from manufacturing experience, further research and data collection, and advances in technology by issuing regulations that set out broad, general categories of manufacturing changes and by using guidance documents to provide FDA's current thinking on the specific changes that fall into those general categories (64 FR 34608 at 34610). FDA has provided recommendations on specific changes in specifications in FDA's guidances entitled "Changes to an Approved NDA or ANDA" and "Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products."

Proposed §§ 314.3(b) and 600.3(ii) defined "validate the effects of the change" as an assessment of the effect of a manufacturing change on the identity, strength, quality, purity, or potency of a drug as these factors relate to the safety or effectiveness of the drug.

(Comment 15) Many comments recommended that FDA replace the terms validate or validation with assess or assessment. Several comments stated that although FDA used the terms consistently with Congress's use of the terms in section 506A of the act, they believe that the term "validate" is likely to cause confusion because this term has long been associated with and has specific meaning under FDA's CGMP regulation.

FDA agrees and has revised the definition as requested by replacing "validate" with "assess." In addition, as a result of comments requesting that the use of the terms drug, drug product, drug substance, and product be standardized, FDA has clarified the definition in § 314.3(b) by replacing the term "drug" with "drug product." FDA has clarified the definition in proposed § 600.3(ii) (new § 600.3(kk)) by replacing the term "drug" with "product." The terms drug product and products are defined at §§ 314.3(b) and 600.3(g), respectively. FDA, on its own initiative, has also revised the phrase "purity, or potency" to "purity, and potency" and the phrase "as these factors relate" to "as these factors may relate" to be consistent with section 506A(b) of the act, and the phrase "to assess the effect" to "to evaluate the effects" for clarity. FDA notes that while the effect of a manufacturing change on the identity, strength, quality, purity and potency of a drug or biological product is to be assessed, this assessment could involve testing of materials directly affected by a change (e.g., drug substance) in addition to or instead of drug or biological product testing.

(Comment 16) Several comments recommended that unambiguous definitions of substantial, moderate, and minimal potential for adverse effects be added to the regulation, and one comment recommended that examples be added for clarification. One comment asked that a definition of natural product be added.

FDA declines to revise the regulation as requested. The regulations apply to many types of changes for a broad spectrum of products. The meaning of substantial, moderate, and minimal potential for adverse effects is most easily illustrated through the use of examples. FDA has decided to use guidance documents to provide specific examples of changes that are considered to have substantial, moderate, and minimal potential to have adverse effect rather than enumerate them in the regulation. FDA has provided many examples of types of changes in FDA's guidances entitled "Changes to an Approved NDA or ANDA" and "Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products." In addition, FDA has provided an explanation of the term "natural products" in the guidance on "Changes to an Approved NDA or ANDA."

(Comment 17) Concerning the regulations on the content and format of an application in § 314.50, one comment noted that § 314.50(d)(1)(i) and (d)(i)(ii) includes the following statement for drug substance and drug product: "Reference to the current edition of the USP/NF [National Formulary] may satisfy the relevant requirements in the paragraph." The comment said it appeared that this statement was being deleted and contended that it should be retained in the regulations.

FDA is clarifying that this sentence has not been deleted from § 314.50(d)(1)(i) or (d)(1)(ii). As stated in the June 1999 proposal, FDA is revising the first two sentences of these paragraphs.

C. Changes to an Approved Application

Proposed § 314.70(a)(1) set forth general requirements under which an applicant must notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application. The notice is required to describe the change fully. Depending on the type of change, the applicant must notify FDA about the change in a supplement under § 314.70(b) or (c) or by inclusion of the information in an annual report under § 314.70(d).

(Comment 18) One comment said that the statements "an applicant must notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application" and that "the notice is required to describe the change fully" should be clarified because it could be overly burdensome from the standpoint that some changes, for example, changes made to batch records submitted as part of the application, may not require reporting under § 314.70.

FDA declines to revise the regulation as requested and notes that the agency does not expect to be informed about nonsubstantive editorial changes in information included in an application. Nonsubstantive editorial changes include such changes as corrections of spelling or typographical errors or reformatting of documents (e.g., batch records, specification sheets).

Proposed §§ 314.70(a)(2) and 601.12(a)(2) (21 CFR 601.12(a)(2)) required the holder of an approved application to validate the effects of manufacturing changes on the identity, strength, quality, purity, or potency of a drug as these factors may relate to the safety or effectiveness of the drug before distributing a drug made with a manufacturing change.

(Comment 19) A few comments said that the proposal would increase the reporting burden despite the specific provision in the Modernization Act for having assessment data at the time of submission of manufacturing change supplements. The comment said that the Modernization Act specifies that a drug made with a manufacturing change may be distributed only after completing studies that assess the effects of the change. The comment said

that the legislative intent of the Modernization Act is that if appropriate studies comparing pre- and postchange material are performed and no evidence of an adverse effect is found, then a reduced reporting category for the evaluated changes is appropriate. The comment reasoned that a given proposed manufacturing change can indeed have substantial potential for adverse effects at its inception because little might be known about the impacts of the change. However, by the time actual material has been made with the change and assessment studies have been successfully completed, most or all of the potential impacts of the change have been eliminated. The comment said that the assessment information should permit a reduced reporting requirement.

FDA disagrees with these comments. Section 506A(c)(2) of the act states that a major manufacturing change is "a change that is determined by the Secretary to have substantial *potential* to adversely affect the identity, strength, quality, purity, or potency of the drug as they may relate to the safety or effectiveness of a drug" (emphasis added). The act bases the reporting category for a change on the potential for that change to have an adverse effect, not on the outcome of the assessment studies. The comment implies that the only changes that would be reported in a prior approval supplement are those where the applicant's studies to assess the effects of the change demonstrate that there is in fact an adverse effect on the identity, strength, quality, purity, or potency of the drug as they may relate to the safety or effectiveness of a drug product. FDA does not believe that this was the intent of Congress. Some manufacturing changes have an adverse effect on the identity, strength, quality, purity, or potency of the drug product. In many cases, the applicant chooses not to implement these manufacturing changes, but sometimes the applicant wishes to do so. If an assessment indicates that a change has adversely affected the identity, strength, quality, purity, or potency of the drug product, the change must be submitted in a prior approval supplement, regardless of the recommended reporting category for the change. For example, a process change recommended for a changes-being-effected-in-30-days supplement could cause the formation of a new degradant that requires qualification and/or identification. The applicant may believe that there are no safety concerns relating to the new degradant. Even so, the applicant must submit this change in a prior approval supplement with appropriate information to support the continued safety and effectiveness of the product. During the review of the prior approval supplement, FDA will assess the impact of any adverse effect on the drug product as this change may relate to the safety or effectiveness of the drug product.

FDA also received comments requesting that the term "assess" be used instead of "validate." FDA has made this change in §§ 314.70(a)(2) and 601.12(a)(2), where appropriate. In § 314.70(a)(2), FDA, on its own initiative, has deleted the phrase "on the identity, strength, quality, purity, and potency of the drug product as these factors may relate to the safety or effectiveness of the drug product" because "assess the effects of the change," as defined in § 314.3(b), includes this phrase.

Proposed §§ 314.70(a)(3) and 601.12(a)(3) stated that notwithstanding the supplement submission requirements, an applicant must make a manufacturing change in accordance with a regulation or guidance that provides for a less burdensome notification of the change.

(Comment 20) Several comments noted that they were pleased that the provision that a change can be made "in accordance with a regulation or guidance that provides for a less burdensome notification of the change" was proposed because it permits less burdensome reporting mechanisms for changes.

FDA acknowledges these comments and has retained this provision in the final rule.

Proposed §§ 314.70(a)(4) and 601.12(a)(4) stated that the applicant must promptly revise all promotional labeling and advertising to make it consistent with any labeling change implemented in accordance with this section.

(Comment 21) Several comments said that the previous provisions in § 314.70 limited the requirement to promptly revise all promotional labeling and advertising to those changes that were to be filed in a changes-being-effected supplement, and that this requirement is not necessary for the type of labeling changes that would be filed in an annual report. The comments suggested that this requirement be limited to those labeling changes that would be filed in supplemental applications.

The agency agrees with the comments and has revised § 314.70(a)(4) to require applicants to revise promotional labeling and advertising to make it consistent with labeling changes implemented in accordance with § 314.70(b) and (c). In addition, § 601.12(a)(4) requires applicants to revise promotional labeling and advertising to make it consistent with labeling changes implemented in accordance with § 601.12(f)(1) and (f)(2).

Proposed § 314.70(a)(5) stated that, except for a supplement providing for a change in the labeling, the applicant must include in each supplemental application providing for a change under paragraph (b) or (c) a statement certifying that a field copy of the supplement has been provided to the applicant's home FDA district office.

(Comment 22) A few comments requested that FDA clarify whether the field copy that is to be sent to the applicant's "home FDA district office" should be the FDA office where the change is being made or the FDA office in the district of the company's corporate headquarters from where the submission documents are sent. The comments also said that if the field copy should be sent to the office where the change is being made, FDA should clarify what FDA office(s) serve for changes made internationally. The comment said that the clarification will help to ensure that the appropriate documents get to the correct FDA district office.

Mailing information for field copies is provided in § 314.440(a)(4). Currently, FDA recommends that the "applicant's home FDA district office" referred to in § 314.440(a)(4) be the district office where the applicant's headquarters is located. FDA has clarified this provision by cross-referencing § 314.440(a)(4). Section 314.440(a)(4) also provides mailing information for international applicants. FDA, on its own initiative, has also clarified the provision by adding "amendments to supplements." A field copy of an amendment to a supplement, which is submitted by an applicant to incorporate additional or corrected information into their original supplement, is currently required under § 314.440(a)(4).

Proposed §§ 314.70(a)(6) and 601.12(a)(5) added a requirement that a list of all changes contained in the supplement or annual report must be included in the cover letter for the supplement or annual report.

(Comment 23) Many comments agreed that a list of changes should be included in the cover letter for a supplement. However, the comments disagreed that a list of all changes contained in the annual report should be included in a cover letter. The comments said that including a list in a cover letter to an annual report is overburdensome because cover letters are not required for annual reports, only a Form FDA 2252, and a list of changes is already provided

in a section of an annual report. Several comments said that an applicant should have the option of providing the list in a location other than the cover letter, such as at the beginning of the supplement.

FDA agrees with the requests to permit the list of changes to be provided in the summary section of the annual report and has revised §§ 314.70(a)(6) and 601.12(a)(5) to require changes to be listed in the cover letter only for supplemental applications.

An annual report is required to contain a brief summary of significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product (§ 314.81(b)(2)(i)). FDA's guidance for industry entitled "Format and Content for the CMC Section of an Annual Report" (September 1994) states, regarding the summary of new information, that the firm should include in the annual report "a brief summary of all changes made to the application during the reporting period including changes made in accordance with approved supplements under 21 CFR 314.70(b) and * * * supplements under 21 CFR 314.70(c)* * *." Supplements are not required to have a summary section (§ 314.50(c)).

FDA is requiring that a list of changes be provided in both supplemental applications and annual reports. FDA proposed this requirement as a means to more efficiently locate and identify changes in what are often documents of substantial length. The list will also allow FDA to quickly assess whether the appropriate reporting category was used. To achieve these objectives, it is essential that the list be in a consistent location for each type of submission.

(Comment 24) Several comments were concerned that the list of changes, if included in a cover letter, would not be considered confidential information.

The standards for disclosing specific information from a cover letter or application do not differ depending on where this information is provided. Information that is exempted from disclosure (e.g., trade secret or confidential commercial information) is not disclosed whether it is in a cover letter or an application (see also §§ 314.430 and 601.51 (21 CFR 601.51)).

(Comment 25) One comment requested that the phrase "list of all changes" be revised to "a brief summary of major changes."

FDA declines to revise the regulation as suggested. Each change, including moderate and minor changes, should be listed. FDA notes that the description of the listed change should be in sufficient detail to allow the agency to quickly determine whether the appropriate reporting category for the change has been used. For example, describing a change as "a change in the drug product specification" does not provide sufficient detail. A description such as "deletion of the friability test and associated acceptance criteria and analytical procedure from the drug product specification" would allow FDA to quickly assess whether the appropriate reporting category was used. The detailed information about each change and the information developed to assess the effects of the change would be provided in the supplement or elsewhere in the annual report.

(Comment 26) Several comments suggested changes in Form FDA 2252 that accompanies an annual report.

FDA declines to revise Form FDA 2252 because it is not within the scope of this regulation.

D. Changes Requiring Supplement Submission and Approval Prior to Distribution of the Product Made Using the Change (Major Changes)

Proposed § 314.70(b)(1) required that a supplement requiring prior approval must be submitted for any change in the product, production process, quality controls, equipment, or facilities that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product.

(Comment 27) Many comments asked whether a prior approval supplement would be required even if the applicant has demonstrated that the change has no significant adverse affect.

Section 506A(c)(2) of the act states that a major manufacturing change is "a change that is determined by the Secretary to have substantial potential to adversely affect the identity, strength, quality, purity, or potency of the drug as they may relate to the safety or effectiveness of a drug." The act bases the reporting category for a change on the potential for that change to have an adverse effect, not on the outcome of the assessment studies. FDA would expect a prior approval supplement to be submitted for a change that has substantial potential to adversely affect the identity, strength, quality, purity, or potency of a drug product even if the applicant concludes that their studies and data demonstrate that the change has no adverse effect. Prior to distribution of the drug product made with the change, FDA must evaluate whether the studies performed by the applicant were sufficient to assess the effect of the change and that the data support the applicant's claim that the change has not adversely affected the identity, strength, quality, purity, or potency of the drug product as they may relate to the safety or effectiveness of a drug product.

(Comment 28) One comment said that section 506A of the act identifies major changes as formulation, specification, or those requiring studies in accordance with part 320 (21 CFR part 320) to demonstrate the equivalence of the drug product to the drug product as manufactured without the change or to the reference listed drug. The comment said that FDA has proposed prior approval supplements for changes that are clearly outside of these three major change categories. Another comment said it appears that FDA has overutilized section 506A(c)(2)(C) of the act.

FDA disagrees that it has overutilized this part of the act. In addition to the three major changes identified previously in this document, section 506A(c)(2)(C) of the act states that a major change "is another type of change determined by the Secretary by regulation or guidance to have a substantial potential to adversely affect the safety or effectiveness of the drug." In previous regulations, many manufacturing changes required prior approval supplements. FDA has used this provision of the act to identify a limited number of changes that it considers to have a substantial potential to adversely affect the identity, strength, quality, purity, or potency of the drug as they may relate to the safety or effectiveness of a drug. The regulation reduces the overall number of supplements requiring FDA approval prior to product distribution. In addition, many changes that are currently reported in supplements will be able to be reported in annual reports. The regulation will not increase the number of annual reports but will allow applicants to include in an annual report information currently required to be reported to the agency in a supplemental application. Moreover, FDA further reduced many reporting requirements from the levels recommended in previous FDA guidances.

Proposed § 314.70(b)(2)(i) provided that, except as provided in § 314.70(c) and (d), prior approval is required for changes in the qualitative or quantitative formulation of the drug, including inactive ingredients, or in the specifications provided in the approved application.

(Comment 29) A few comments recommended that proposed

§ 314.70(b)(2)(i) be revised to better reflect section 506A(c)(2)(A) of the act which allows exceptions to the requirement to obtain prior approval before changing the qualitative or quantitative formulation of the drug. One comment recommended the provision be revised to state: "Except as provided in paragraphs (c) and (d) of this section or exempted by regulation or guidance * * *."

FDA declines to revise the regulation as requested. Section 506A(c)(2)(A) of the act states that a prior approval supplement is required when a change "is made in the qualitative or quantitative formulation of the drug involved or the specifications in the approved application or license * * * (unless exempted by the Secretary by regulation or guidance * * *)." Proposed § 314.70 is consistent with the provisions of the act. Exemptions by regulation are provided in § 314.70(c) or (d). This language is already included in § 314.70(b)(2)(i). In addition, FDA may use guidance documents to provide for a less burdensome notification of a specific change. This exemption is included in § 314.70(a)(3) and applies to § 314.70(b)(2)(i) as well as the other changes listed in § 314.70.

(Comment 30) Several comments noted that the SUPAC guidances allowed for some changes in qualitative or quantitative formulation of the drug product to be filed in changes-being-effected supplements or annual reports. One comment said that the regulations should follow the standards in the SUPAC guidances.

FDA has not incorporated the qualitative and quantitative formulation change information from the SUPAC guidances in the regulation because, as stated in the proposal, the agency's approach is to issue regulations that set out broad, general categories of manufacturing changes and use guidance documents to provide FDA's current thinking on the specific changes included in those categories.

(Comment 31) Several comments said that changes in specification to comply with an official compendium should not require prior approval supplements.

FDA is not requiring prior approval supplements for specification changes made to comply with an official compendium. A complete discussion of this issue is provided under section III.F of this document, "Changes To Be Described in the Next Annual Report," in response to comments on § 314.70(d)(2)(i).

(Comment 32) One comment recommended the proposed language be revised to limit specification changes to those for drug substance or drug product.

FDA considers a specification to be a quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, components, in-process materials, container closure systems, or other materials used in the production of a drug substance or drug product. Therefore, FDA declines to revise the proposal as suggested.

Proposed § 314.70(b)(2)(ii) required prior approval for changes requiring completion of studies in accordance with part 320 to demonstrate the equivalence of the drug to the drug as manufactured without the change or to the reference listed drug.

(Comment 33) One comment said that reference to part 320 suggests that bioequivalence must be addressed for "a change in the manufacturing process * * *." The comment said that this will lead to significant interpretation issues. The comment said that a selective subset of major manufacturing changes that truly have "substantial potential" should be specified here. Another comment said that when the product is a true solution, changes to the manufacturing process (not formulation) are highly unlikely to change the formulation and additional clinical (bioequivalence) studies should not always be required.

FDA declines to revise the proposal based on these comments. The requirements for when a study is needed to demonstrate the equivalence of a drug product made with the proposed change to a drug product made without the change or to the reference listed drug are provided in part 320. Part 314 is not intended to supplement, supersede, or clarify these requirements. Section 314.70(b)(2)(ii) specifies only that if such a study is required under part 320 to support a postapproval change, the postapproval change must be submitted using a prior approval supplement. Changes that require a study under part 320 are considered major changes that have a significant potential to affect the identity, strength, quality, purity, or potency of the product as it relates to the safety or effectiveness of a product, and FDA would need to review such studies before a product made with the change is placed into distribution.

Proposed § 314.70(b)(2)(iii) required prior approval for changes that may affect product sterility assurance, such as changes in product or component sterilization method(s) or an addition, deletion, or substitution of steps in an aseptic processing operation.

(Comment 34) Many comments stated that the proposed language was too broad and should be modified to state "changes that may significantly affect product sterility assurance" or "changes that significantly affect product sterility assurance". One comment said that the term "may affect" is not appropriate because any change may affect one or more attributes of a sterile drug.

Sterility of drug products or drug substances is a fundamental and essential quality attribute of these drugs and is a critical aspect of the safety assessment. The manufacture of a sterile drug is an exacting, difficult, and highly controlled series of processes, especially in the case of aseptically processed drugs. The concept of significance or "significantly affect" implies that a measurement of an attribute, such as sterility, can be made. However, no test is sensitive enough to detect unacceptable sterility assurance levels (i.e., the probability of a nonsterile unit). For example, a batch of drug product tested using the standard drug product sterility test described in the USP/NF will fail the sterility test only when at least 14 percent of the batch is contaminated (95 percent confidence level). This sterility assurance level is unacceptable. The probability of nonsterile units for terminally sterilized and aseptically processed drugs is normally expected by FDA to be less than 0.0001 percent and 0.1 percent, respectively. FDA ensures the safety of sterile drugs by assessing the efficacy of a given sterilization process for a specific drug and by ensuring that the facilities producing sterile drugs comply with CGMPs. The assessment of the efficacy of a sterilization process includes review of multiple protocols and scientific experiments designed to demonstrate that the sterilization process and associated control procedures can reproducibly deliver a sterile product. The data derived from the experiments and control procedures allow certain conclusions to be drawn about the probability of nonsterile units. A properly validated sterilization process will provide the sterility assurance level required by FDA to ensure the safety of sterile drugs. Because of the lack of adequate test procedures for assessing sterility and the complexity in evaluating the process validation and controls information to determine the level of sterility assurance that a given process provides for a specific drug, FDA has used the term "may affect" and declines to revise the proposal as suggested.

(Comment 35) Many comments stated that the proposed language should be clarified to state "changes that may adversely affect product sterility assurance * * *" or "changes that may reduce (or decrease) product sterility assurance * * *".

New § 314.70(b)(1) already identifies that the changes that should be submitted in prior approval supplements are those that have a substantial potential to have an "adverse effect." FDA declines to revise proposed § 314.70(b)(2)(iii) as requested because the addition of the term "adversely" is redundant. FDA emphasizes that the assessment of whether a change may adversely affect sterility assurance is a complex and multidimensional analysis. For example, a change to a more stringent terminal sterilization process, while in theory providing a lower probability of nonsterile units, may damage the container closure system so that sterility of individual units could not be maintained.

(Comment 36) Several comments said that the proposed language is too restrictive because it indicates that all changes to sterile products should be submitted in prior approval supplements. The comments said that this contradicts what is in the guidance entitled "Changes to an Approved NDA or ANDA," which identifies some changes that do not have to be filed in prior approval supplements. One comment identified specific examples of manufacturing changes for sterile products and said that these should not be considered major changes.

FDA considers changes that may affect the sterility assurance level of a drug to have significant potential to affect the safety of the drug. Therefore, FDA has identified this change as one that requires prior approval. As stated in the June 1999 proposal, this rulemaking sets out broad, general categories of manufacturing changes, and the agency uses guidance documents to provide FDA's current thinking on the specific changes included in those categories. Under § 314.70(a)(3), an applicant must notify FDA of a manufacturing change in accordance with either a regulation or a guidance that addresses the same issues as the regulation but that provides for a less burdensome notification of the change than the regulation (for example, by submission of a supplement that does not require approval prior to distribution of the product). For example, in the guidance entitled "Changes to an Approved NDA or ANDA," FDA has identified less burdensome reporting categories for certain changes that it believes have less potential to affect sterility assurance and consequently the safety of the drug.

(Comment 37) A few comments said that this provision increases the regulatory burden with respect to sterile products. The comments said that only fundamental changes to sterile processing require prior approval.

FDA disagrees with this comment. Under the previous regulations at § 314.70, manufacturing site, processing, and packaging changes for sterile drugs almost always required a prior approval supplement (previous § 314.70(b)(1)(iv), (b)(1)(v), (b)(2)(iv), (b)(2)(v), and (b)(2)(vi)). Under § 314.70(c) and (d), certain changes related to sterile drugs may be submitted in changes-being-effected supplements or annual reports (for example, § 314.70(d)(2)(i) and (iii)). In the guidance entitled "Changes to an Approved NDA or ANDA," FDA has identified many changes related to sterile drugs that may now be submitted in changes-being-effected supplements or annual reports.

Proposed § 314.70(b)(2)(iv) required prior approval for changes in the synthesis or manufacture of the drug substance that may affect the impurity profile and/or the physical, chemical, or biological properties of the drug substance.

(Comment 38) One comment said that the proposal should be revised to state "Changes in the route of synthesis or * * *." Changes such as an additional recrystallization step (using the same solvents, and so forth) should be considered for changes-being-effected status.

FDA declines to revise the proposal as suggested. Changes in the synthesis, including the route of synthesis, may have an effect on the impurity profile and/or the physical, chemical, or biological properties of the drug substance. For example, a change in a solvent used in the crystallization step may affect the impurity profile and physical properties of the drug substance even though this change would not be considered a change in the "route of synthesis."

(Comment 39) Several comments stated that the proposed language should be clarified to state "changes that may adversely affect the impurity profile * * *" because changes that improve the quality of the drug substance should not require a prior approval supplement.

New § 314.70(b)(1) states that the changes that should be submitted in prior approval supplements are those that have a substantial potential to have an "adverse effect." FDA declines to revise the provision as requested because the addition of the term "adversely" is redundant.

(Comment 40) One comment suggested that FDA change "may affect the impurity profile of the drug product" to "are likely to affect the impurity profile of the drug product." The comment said that many factors could affect the impurity profile, and this stringent reporting requirement should be reserved for factors that are likely to produce a change.

FDA believes the phrase "may affect" is appropriate because the decision on whether a change should be considered a major, moderate, or minor change is based on the potential for the change to adversely affect the identity, strength, quality, purity, or potency of the drug as they may relate to the safety or effectiveness of a drug product. FDA considers a change that "may affect the impurity profile and/or the physical, chemical, or biological properties of the drug substance" to be a change that has a substantial potential to result in an adverse effect and declines to delete "may."

(Comment 41) One comment said that inserting the clause "beyond those studied in the pre-clinical studies and requiring a change in the approved specifications" after impurity profile would add clarity. The comment said that according to the ICH guidance entitled "Impurities in New Drug Substances" (ICH Q3A), impurities below a certain threshold would not necessarily require registration.

The process of qualifying impurities and determining if a postchange impurity profile for a drug substance is equivalent or better than the impurity profile of the prechange material is a complex issue. FDA does not believe it is possible to clarify the regulations to adequately address the many different types of human drugs it regulates. For example, not all drug approvals require preclinical studies. FDA declines to revise the proposal as suggested. FDA published the BACPAC I guidance to provide recommendations on how to evaluate changes in impurity profiles.

(Comment 42) Several comments said that the proposed regulations were not consistent with the BACPAC I guidance. Several comments said that the proposal was much more restrictive than what was included in the BACPAC I guidance. One comment said that changes in drug substance synthesis route, which occur prior to the formation of key intermediates, should not be regarded as major changes, since the potential to impact the quality, strength, identity, and purity of the final product is low.

FDA declines to revise the regulations as requested. The BACPAC I guidance is an example of a guidance that permits certain specific changes that fall under the general category of a change that "may affect the impurity profile and/or the physical, chemical, or biological properties of the drug substance" to be reported using a less burdensome method of notification. Under § 314.70(a)(3), an applicant must notify FDA of a manufacturing change in accordance with either a regulation or a guidance that addresses the same issues as the regulation but that provides for a less burdensome notification of the change than the regulation (for example, by submission of a supplement that does not require approval prior to distribution of the product).

Proposed § 314.70(b)(2)(v) required prior approval for changes in labeling, except those described in § 314.70(c)(6)(iii), (d)(2)(ix), or (d)(2)(x).

On its own initiative, FDA has revised § 314.70(b)(2)(v) to add: "If applicable, any change to a Medication Guide required under part 208 of this chapter, except for changes in the information specified in § 208.20(b)(8)(iii) and (b)(8)(iv) of this chapter." This provision, which was previously in § 314.70(b)(3)(ii), was inadvertently omitted from the proposed rule.

(Comment 43) Many comments said that FDA should clarify "labeling" to indicate "drug product labeling" because drug substance labeling changes need not be submitted.

FDA declines to revise the regulations as requested. The term "labeling" in § 314.70 is consistent with "labeling" as used in part 201 (21 CFR part 201). Part 201 applies to the labeling of drugs and/or drug products.

Proposed § 314.70(b)(2)(vi) required prior approval for changes in a container closure system that controls drug delivery or that may affect the impurity profile of the drug product.

(Comment 44) Several comments requested that the proposed language be clarified to state "changes that may adversely affect the impurity profile * * *" or "changes that adversely affect the impurity profile ***."

FDA declines to revise the provision because the addition of the term "adversely" is redundant. New § 314.70(b)(1) already states that the changes that should be filed in prior approval supplements are those that have a substantial potential to have an "adverse effect." FDA believes the phrase "may affect" is appropriate because the decision on whether a change should be considered a major, moderate, or minor change is based on the potential for the change to adversely affect the identity, strength, quality, purity, or potency of the drug as they may relate to the safety or effectiveness of a drug product. FDA considers a change that "may affect the impurity profile of the drug product" to be a change that has a substantial potential to result in an adverse effect and declines to delete "may."

(Comment 45) One comment requested clarification of what is meant by "controls drug delivery," such as quantity dispensed, machine calibration, and volume of fill.

For some drug products, the container closure system itself, rather than a person, regulates the amount of drug product that is administered to a patient. These container closure systems are considered to "control drug delivery." For example, a patient that uses a metered dose inhalation product as instructed cannot control the amount of drug product the container closure system delivers or verify that the appropriate amount has been administered. Where a drug product container closure system controls drug delivery, FDA requires information to be submitted to support that the container closure system can accurately and repeatedly deliver the required amount of drug product. The design and operation of these container closure systems is critical to ensure that the patient receives the correct dose. A drug product may not be safe or effective if a patient receives too much or too little of the drug product. Changes in these systems are considered to have a substantial potential to adversely affect the identity, strength, quality, purity, or potency of the drug as they may relate to the safety or effectiveness of a drug product. Container closure systems for drug products where a person controls the amount of drug product administered and/or which allow for verification that the appropriate amount has been administered (e.g., number of tablets, milliliters of liquid) are not considered container closure systems that "control drug delivery."

(Comment 46) Another comment asked whether this section specifically refers to the final packaged product only.

Changes in "a container closure system that controls drug delivery" applies only to the marketed drug product container closure system, and the language has been revised in the final rule to clarify this. Changes that "may affect the impurity profile of the drug product" applies to any type of container closure system.

(Comment 47) One comment noted an apparent conflict between § 314.70(b)(2)(vi), which says that a "change in a container closure system that * * * may affect the impurity profile of the drug product" should be submitted in a prior approval supplement and § 314.70(c)(2)(i), which says that "a change in the container closure system that does not affect the quality of the final drug product" should be submitted in a changes-being-effected-in-30-days supplement. The comment said that this would allow for inconsistent and overly conservative interpretations of what might fall into this latter category.

FDA agrees that clarification of the wording in these two provisions of the regulations is needed. FDA has particular concerns about changes in the type (e.g., glass to high density polyethylene (HDPE), HDPE to polyvinyl chloride, vial to syringe) or composition (e.g., one HDPE resin to another HDPE resin) of packaging components because these changes may affect the impurity profile of the drug product. These concerns are compounded by the fact that, in most cases, the packaging component manufacturer considers the manufacturing process confidential information and discloses it only to FDA. Therefore, an applicant does not have knowledge of all potential impurities that a different type or composition of a packaging component may introduce into a product. Depending on the dosage form affected and its route of administration, FDA may have to evaluate the safety of changes in the type or composition of a packaging component. Because of the safety concerns relating to new impurities from a packaging component with this type of change, FDA considers such changes to have a substantial potential to adversely affect the identity, strength, quality, purity, or potency of the drug as they may relate to the safety or effectiveness of a drug product. FDA has revised § 314.70(b)(2)(vi) to limit the requirement to situations involving changes in the type or composition of a packaging component. FDA considers a deletion or addition of a packaging component to fall within the meaning of a change in the type of packaging component. FDA may, through regulations or guidance, identify certain dosage forms and/or routes of administration where there is a lower potential for adverse effect and allow changes in type or composition of a packaging component in these situations to be reported in changes-being-effected supplements or annual reports.

For consistency with the proposal, FDA has revised § 314.50(d)(1)(ii)(*a*) to

change "containers and closure systems" to "container closure systems."

Proposed § 314.70(b)(2)(vii) required prior approval for changes solely affecting a natural product, a recombinant DNA-derived protein/polypeptide product, or a complex or conjugate of a drug with a monoclonal antibody for the following:

(1) Changes in the virus or adventitious agent removal or inactivation method(s); (2) changes in the source material or cell line; and (3) establishment of a new master cell bank or seed.

(Comment 48) Several comments requested that FDA delete the reference to "natural products," while others requested that FDA provide a definition for natural products. A few comments asked whether fermentation-based products are considered natural products.

FDA declines to delete natural products from this provision. The changes identified in this provision are considered to be major changes and apply equally to a natural product, a recombinant DNA-derived protein/polypeptide, or a complex or conjugate of a drug substance with a monoclonal antibody. FDA has provided a definition of natural product in the guidance entitled "Changes to an Approved NDA or ANDA" but declines to provide the definition in the regulation because advancements in technology may require that the definition be revised. FDA has defined natural product in the guidance to mean "materials (e.g., drug substance, excipients) that are derived from plants, animals, or microorganisms. The specific recommendations for natural products are not applicable to inorganic compounds (e.g., salts, minerals)." Fermentation based products are considered natural products.

(Comment 49) A few comments said that this provision increases the regulatory burden with respect to natural products. One comment said that there was no need to distinguish a natural product, a recombinant DNA-derived protein/polypeptide, or a complex or conjugate of a drug substance with a monoclonal antibody from other products.

FDA disagrees with these comments. Under the previous regulations at § 314.70, many manufacturing process changes for drug substances and drug products, including those for a natural product, a recombinant DNA-derived protein/polypeptide, or a complex or conjugate of a drug substance with a monoclonal antibody, required a prior approval supplement (previous § 314.70(b)(1)(iv) and (b)(2)(v)). FDA has reduced the reporting category for many manufacturing process changes relating to these products by allowing them to be reported in changes-being-effected supplements or annual reports. However, the three changes specified in this provision, which are unique to these specific types of drugs, are considered to have a substantial potential to adversely affect the identity, strength, quality, purity, or potency of the drug product as they may relate to the safety or effectiveness of a drug product. Virus or adventitious agent removal or inactivation processes are the means by which FDA ensures that adventitious agents such as porcine parovirus, if present, are removed. Failure to remove such adventitious agents has a significant potential to adversely affect public safety. Changes in source material or cell line and establishment of a new master cell bank or seed have a substantial potential to affect the quality of a drug substance. For example, a change in source material (e.g., species, geographic region of harvesting) could result in different impurities or contaminants (e.g., pesticides) than were previously seen or a change in potency.

Proposed § 314.70(b)(3) stated that the applicant must obtain approval of a supplement from FDA before distributing a product using a change and specified the information to be included in the supplement.

(Comment 50) A few comments requested adding "as appropriate" as follows: "Except for submissions under paragraph (e) of this section, the following shall be contained in the supplement, as appropriate." The comments said that not all listed material is relevant for every submission.

FDA declines to revise the provision as requested. FDA expects that the information specified in § 314.70(b)(3)(i) through (b)(3)(v) will be needed for almost all supplemental applications. FDA believes that the addition of "as appropriate" may incorrectly give the impression that this information is not routinely needed and would result in supplemental applications being submitted with insufficient information. FDA may specify in a guidance that information required in § 314.70(b)(3)(i) through (b)(3)(v) is not needed for a particular change. However, in the absence of such a recommendation, FDA would expect § 314.70(b)(3)(i) through (b)(3)(v) to be addressed in each supplemental application. The information in § 314.70(b)(3)(vi) and (b)(3)(vii) is needed only in certain situations, and this is clearly indicated.

Proposed § 314.70(b)(3)(vi) stated that for a natural product, a recombinant DNA-derived protein/polypeptide product, or a complex or conjugate of a drug with a monoclonal antibody, relevant validation protocols must be provided in addition to the requirements in § 314.70(b)(3)(iv) and (b)(3)(v).

(Comment 51) One comment said that the requirement that relevant validation protocols be provided is overly restrictive and burdensome. The comment suggested that this statement be rephrased to state "validation protocols may be requested by the FDA." Another comment recommended that this section be deleted because there is no need for different requirements for these products. The comment said that this information (relevant validation protocols) is available for review onsite. The comment said that if FDA disagrees and feels that special requirements are warranted, the comment recommended these specific details be more appropriately captured in the guidance instead.

Unless otherwise specified by FDA, validation protocols and data need not be filed in the application. For most products, FDA does not require the submission of validation protocols and data. However, for a natural product, a recombinant DNA-derived protein/polypeptide, or a complex or conjugate of a drug substance with a monoclonal antibody, FDA does require the submission of validation protocols for certain critical manufacturing processes unique to these drug substances and drug products. For example, FDA would expect the validation protocol for the virus or adventitious agent removal or inactivation process to be submitted in an application. FDA currently requires this type of information to be submitted in an application and believes it is necessary; therefore, FDA declines to revise the regulation as suggested.

Proposed § 314.70(b)(3)(vii) stated that for sterilization process and test methodologies, relevant validation protocols must be provided in addition to the requirements in § 314.70(b)(3)(iv) and (b)(3)(v).

(Comment 52) One comment said that the inclusion of validation protocols for sterilization assurance is new. The comment also said that submitting all validation data is different from data summaries previously requested and provided for microbiological consults.

FDA disagrees with this comment. The information on sterility assurance FDA expects an applicant to provide in an application and the format of the data are described in the guidance

entitled "Submission of Documentation of Sterilization Process Validation in Applications for Human and Veterinary Drug Products." The provisions of § 314.70(b)(3)(vii) are consistent with current FDA policy.

(Comment 53) One comment said that clarification is needed that the test methodologies and validation protocols referred to in this section are for the sterilization process only.

FDA agrees and has replaced "test methodologies" with "test methodologies related to sterilization process validation" in new § 314.70(b)(3)(vii).

Proposed § 314.70(b)(3)(viii) stated that a reference list of relevant SOPs, when applicable, must be contained in the supplement.

(Comment 54) Many comments recommended that reference to SOPs be deleted. Several of these comments said that it was unclear what value a reference list of SOPs provides in the division review process and that SOPs are generally considered a CGMP issue. One comment said that reference to appropriate SOPs is currently required only as it pertains to sterilization processes and biologic products. The comment also contended that inclusion of a reference list of SOPs in the submission for any type of change is not necessary. Several comments said that "when applicable" was too vague and one comment recommended that the provision be revised to state "A reference list of relevant standard operating procedures (SOPs) for aseptic processing operations."

An applicant is required to submit a "full description of controls used for the manufacture, processing, and packing of a drug" (section 505 of the act). This information may be submitted in different forms, including SOPs. In most cases, SOPs do not include information relevant to the NDA or ANDA review, but rather information relevant to determining an applicant's compliance with CGMPs. However, in the case of a natural product, a recombinant DNA-derived protein/polypeptide, a complex or conjugate of a drug substance with a monoclonal antibody, or a sterilization process, information contained in SOPs is often relevant to the review of certain aspects of an application. FDA has deleted proposed § 314.70(b)(3)(viii) and revised § 314.70(b)(3)(vi) and (b)(3)(vii) to limit the need for information on SOPs in these situations. The agency clarifies that information regarding SOPs is needed in some cases. FDA wishes to emphasize that while the information is needed for the application review, it is not always necessary to submit the actual SOP as long as the required information is provided in sufficient detail as part of the application.

On its own initiative, FDA has revised § 314.70(b)(3)(iv) by replacing the phrase "evaluate the effect of the change * * * (validating the effects of the change)" with "assess the effects of the change" because the term is defined at § 314.3(b). In the introductory text of § 314.70(b)(3), FDA replaced the phrase "the following shall" with "the following information must" to add clarity.

Proposed §§ 314.70(b)(4) and 601.12(b)(4) provided that an applicant may request an expedited review of a supplement if a delay in making the change would impose an extraordinary hardship or for public health reasons.

(Comment 55) One comment said that a complete definition of expedited review from FDA's "Manual of Policies and Procedures" (MAPPs) should be incorporated in the regulation. One comment said FDA should consider adding mandatory vendor-imposed changes (without sufficient reaction time) to the list of "not reasonably foreseen" events.

FDA has published two MAPPs on expedited review—MAPP 5420.1 entitled "Requests for Expedited Review of Supplements to Approved ANDAs and AADAs" and MAPP 5410.3 entitled "Requests for Expedited Review of NDA Chemistry Supplements." These MAPPs contain criteria that FDA uses in granting expedited review based on public health need, extraordinary hardship on the applicant, or agency need. FDA declines to add this detailed information on internal FDA procedures to the regulation but encourages applicants to review these MAPPs to see how FDA would assess a request for an expedited review. The MAPPs already include "abrupt discontinuation of supply of active ingredient, packaging material, or container closure" as an example of an extraordinary hardship that was not reasonably foreseen. An applicant is required to submit sufficient documentation to support a need for an expedited review. In the case of an abrupt discontinuation of supply, FDA will require information to support that the discontinuation was abrupt such as when the supplier informed the applicant of the discontinuation of supply, the amount of supplies available in-house and from the supplier, and the date the supplies are expected to run out. FDA emphasizes that inadequate planning on the part of an applicant is not a reason for FDA to expedite the review of a supplement based on extraordinary hardship.

(Comment 56) A few comments requested that FDA provide feedback to the sponsor on acceptance or refusal of an "expedited review" request within 30 days.

FDA's MAPPs 5240.1 and 5310.3 describe procedures for processing expedited review requests. All requests for expedited review are reviewed promptly, usually within 30 days of receipt. If the review division denies the request, the applicant will be contacted. FDA declines to specify that it will contact applicants to advise them that their expedited review request has been granted or that the decision will be made within 30 days. However, applicants can contact the review division at any time about the status of their request.

E. Changes Requiring Supplement Submission at Least 30 Days Prior to Distribution of the Drug Product Made Using the Change (Moderate Changes)

Proposed § 314.70(c)(1) required that a supplement be submitted for any change in the product, production process, quality controls, equipment, or facilities that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product. If the change concerns labeling, 12 copies of the final printed labeling must be included.

(Comment 57) One comment said that in the preamble to the final rule, FDA should further clarify the criteria to be used to distinguish between changes-being-effected supplements that can be implemented immediately and those where distribution cannot occur until 30 days after FDA receives the supplement.

The decision by FDA as to whether a moderate change should be classified as one that can be implemented by an applicant when FDA receives a supplement or one requiring supplement submission at least 30 days prior to distribution of the drug product made using the change depends on many factors. Some of these factors include the need for FDA to verify compliance status, dosage form, route of administration, or whether, based on FDA's experience, a particular type of change is usually complete and provides the proper information. It is not possible to provide a general list of factors considered because different factors are considered by FDA for each type of change.

(Comment 58) A few comments requested changes in the format of this section. One comment said that supplements for changes being effected in 30 days as well as changes being

effected immediately are defined as "moderate changes." The comment asked whether there can be different verbiage for these two categories to allow differentiation. Another comment suggested that the two types of changes-being-effected supplements should be separated into different paragraphs under this section.

FDA declines to revise the regulations as requested. FDA believes that the format and terms are adequate and will not be unclear when individuals become more familiar with the regulations and the guidance.

(Comment 59) One comment said it recognizes that the supplements for changes being effected in 30 days is a statutory classification. The comment said that, unfortunately, the provision does not provide material advantage over a changes-being-effected supplement for either the agency or the industry, especially for new chemical entities (NCEs). The comment said that, instead, the provision adds a 30-day wait period that does not currently exist for NCEs. The comment said that, from FDA's point of view, the reviewer will be spending twice the amount of time on the same application, first for an administrative review for the completeness of the information and later to actually review the application. The comment said that from industry's point of view, the 30-day wait period does not necessarily provide increased assurance of an approval action. The comment suggested that any change that can be the subject of a changes-being-effected-in-30-days supplement could just as easily be reclassified as a changes-being-effected supplement. The comment said that this would save time for both FDA and industry.

FDA declines to revise the regulation as requested. The changes-being-effected-in-30-days provision allows certain changes previously requiring prior approval to be implemented rapidly, thus reducing the percentage of supplements requiring prior approval. FDA recognizes that the public health can be adequately protected without requiring approval of certain manufacturing changes prior to distribution of the product made with the change. FDA continues to believe that it is important that such changes be documented and validated so there is a mechanism for assessing the consequences of the changes and that the agency approve such changes. Ready access to information regarding such changes through submission of a supplement 30 days before distribution of the product would protect against the distribution of unsafe or ineffective products while speeding the availability of improved products. The provision is intended to benefit the public health because it permits FDA to stop or delay a product from being distributed to the public when the product is made with a major change (i.e., one with a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product) that is improperly categorized as a moderate change. The provision also permits the agency to act when information necessary to demonstrate that the change has not adversely affected product quality is not provided.

(Comment 60) Several comments recommended inserting "only" in the last sentence to read: "If the change concerns only labeling, include 12 copies of final printed label." One comment said that there are changes that have minor impacts on labeling (for example, signature changes) that, if implemented as stated, would result in an increased regulatory burden to provide finished product labeling prior to change implementation.

FDA declines to revise the regulation as requested because changes-being-effected supplements (within 30 days and immediately) that include both manufacturing changes and labeling changes must also include 12 copies of the final printed labeling, if appropriate. However, FDA has clarified that the only labeling changes that require submission of 12 copies of finished product labeling at the time of supplement submission are those classified as a moderate change. Changes-being-effected manufacturing supplements that result in labeling changes that are classified as minor under § 314.70(d) do not have to include copies of final printed labeling. The final printed labeling for these minor labeling changes can be submitted in the next annual report in accordance with § 314.81(b)(2)(iii).

FDA has clarified § 314.70(c)(1) to explain when final printed labeling must be submitted by revising the last sentence to read "If the supplement provides for a labeling change under paragraph (c)(6)(iii) of this section, 12 copies of the final printed labeling must be included."

(Comment 61) One comment said that FDA should delete the requirement to provide 12 copies of the final printed labeling with a changes-being-effected labeling supplement. The comment said that although the specified changes may be submitted in a changes-being-effected supplement, at times they may not be implemented until after the submission. The comment said that to print final labeling specifically for the changes-being-effected supplement is unnecessarily expensive and complicates the normal labeling printing process. The comment said that an alternative would be to submit a typed copy of the labeling and submit the final printed labeling in the annual report.

FDA declines to revise the regulation as requested. Moderate labeling changes, which are those that have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product, can be implemented immediately without FDA's prior approval. In FDA's experience, errors that occurred when draft labeling was converted to final printed labeling have made the final printed labeling unacceptable. Also, FDA reviews not only the content of labeling for accuracy but also the format (e.g., layout, size of print) for clarity. A typed copy of the labeling does not always accurately reflect the format of the final printed labeling. The labeling should be available for review at the time of submission whether or not the applicant intends to implement the change immediately upon FDA receipt of the supplement.

(Comment 62) One comment stated that current § 314.70(c)(3) permits a different facility to be used for the production of the drug substance under certain conditions. The comment said that the proposal does not include this provision, and that FDA intends to provide recommendations concerning this in certain guidance documents. The comment said that this provision of current § 314.70 should be retained in the revised regulation because the industry is familiar with the provision and has used it for years.

FDA declines to revise the proposal as requested. As stated in the proposal, the agency's approach is to issue regulations that set out broad, general categories of manufacturing changes and use guidance documents to provide FDA's current thinking on the specific changes included in those categories. FDA has provided recommendations on changes in manufacturing sites in FDA's guidance entitled "Changes to an Approved NDA or ANDA."

Proposed § 314.70(c)(2)(i) stated that changes requiring supplement submission at least 30 days prior to distribution of the drug product made using the change (moderate changes) includes the following change: A change in the container closure system that does not affect the quality of the final drug product.

(Comment 63) Many comments recommended that the requirement should be changed to include "significant change" and/or "adversely affect," so that the regulation would read: "A significant change in the container closure system that does not adversely affect the quality of the final drug product."

FDA declines to revise the provision as requested. New § 314.70(c)(1) already states that the changes that should be filed in changes-being-effected supplements are those that have a moderate potential to have an "adverse effect." Adding the word "adversely" to this provision is redundant. Adding the term "significant" is also inappropriate because any change, whether big or small, should not adversely affect the quality of the final drug product. Some manufacturing changes have an adverse effect on the identity, strength, quality, purity, or potency of the drug product. In many cases, the applicant chooses not to implement these manufacturing changes, but sometimes the applicant wishes to do so. If an assessment indicates that a change has adversely affected the identity, strength, quality, purity, or potency of the drug product, the change should be submitted in a prior approval supplement, regardless of the recommended reporting category for the change. For example, a process change recommended for a changes-being-effected-in-30-days supplement could cause the formation of a new degradant that requires qualification and/or identification. The applicant may believe that there are no safety concerns relating to the new degradant. Even so, the applicant should submit this change in a prior approval supplement with appropriate information to support the continued safety and effectiveness of the product. During the review of the prior approval supplement, FDA will assess the impact of any adverse effect on the drug product as this change may relate to the safety or effectiveness of the drug product.

(Comment 64) One comment noted an apparent conflict between proposed § 314.70(b)(2)(vi), which stated that a "change in a container closure system that * * * may affect the impurity profile of the drug product" should be filed in a prior approval supplement, and proposed § 314.70(c)(2)(i), which stated that "a change in the container closure system that does not affect the quality of the final drug product" should be filed in a changes-being-effected-in-30-days supplement. The comment said that this would allow for inconsistent and overly conservative interpretations of what might fall under § 314.70(b)(2)(vi).

FDA agrees and has clarified the wording in these two provisions. Changes to proposed § 314.70(b)(2)(vi) were discussed previously under section III.C of this document. For consistency, § 314.70(c)(2)(i) was revised to exclude changes that would be included under § 314.70(b) and (d).

FDA emphasizes that the container closure system and packaging component changes identified in § 314.70(b) must be filed in a prior approval supplement even if an applicant concludes that the quality of the drug product has not been adversely affected. The provision has also been revised to standardize terminology, as requested, by changing "final drug product" to "drug product."

Proposed § 314.70(c)(2)(ii) stated that changes requiring supplement submission at least 30 days prior to distribution of the drug product made using the change (moderate changes) included the following change: Changes solely affecting a natural protein product, a recombinant DNA-derived protein/polypeptide product or a complex or conjugate of a drug with a monoclonal antibody, including the following: (1) An increase or decrease in production scale during finishing steps that involves new or different equipment; and (2) replacement of equipment with that of similar, but not identical, design and operating principle that does not affect the process methodology or process operating parameters.

(Comment 65) Several comments said that having special requirements for this category of products represents additional regulatory reporting requirements beyond current practice. A few comments recommended that this section be deleted. One comment said that these products should not be regulated differently than the traditional products. The comment said that if FDA disagrees and feels that this requirement is warranted, the specific details be captured in the guidance instead.

FDA declines to revise the regulation as requested. There are specific issues and concerns relating to the production of proteins that are not routinely associated with other classes of drugs; therefore, FDA has specified certain requirements for proteins. Proteins are susceptible to denaturation. Denaturation can be caused by changes in sheer force as a result of scale and/or equipment changes. Also, proteins differentially adsorb to surfaces. The identity, strength, quality, purity, or potency of the product could be affected by changes in scale or equipment because of these characteristics.

(Comment 66) A few comments requested that FDA clarify whether this section applies to drug products or drug substance.

FDA agrees and has clarified the proposed language, which is intended to apply to both drug substance and drug product.

(Comment 67) A few comments recommended that FDA delete reference to "natural protein products." The comments also requested clarification as to whether the definition natural products includes fermentation products.

FDA declines to revise the regulation as requested. Issues about scale and equipment and concerns associated with proteins are the same whether the protein is derived from a natural source or by other means, such as DNA technology. The definition of natural products was discussed in comment number 48 of this document. Natural proteins are a subset of natural products.

(Comment 68) One comment said that this section applies to both an increase and decrease in batch size involving new equipment. The comment asked whether new equipment includes replacement equipment.

FDA agrees and has clarified the proposed language. The phrase "new or different equipment" has been replaced by the phrase "different equipment." Different equipment can include new models, changes in capacity, construction materials (e.g., glass-lined tanks to stainless steel), equipment design, and/or equipment operating principles. If a scale change involves replacing equipment with equipment that is identical in all critical aspects (e.g., same model and capacity, same construction materials), this is a type of change that could be reported in an annual report. For the same reasons, FDA is revising § 601.12(c)(2)(ii) to delete the word "new."

(Comment 69) A few comments requested clarification of "finishing steps."

FDA declines to revise the regulations to provide clarification of the term "finishing steps." In general, finishing steps are considered those steps in the manufacturing process where the stability, or the property and performance, of a protein product is less likely to be affected by changes in scale or equipment. The steps in a manufacturing process that would be considered finishing steps depend on the manufacturing process and the specific protein being manufactured. A particular manufacturing step may be

considered a finishing step for one product but not for another. An applicant is encouraged to discuss with FDA which steps would be considered finishing steps for a particular product and process. This discussion should occur as early in the process as possible, including during investigational new drug (IND) meetings.

(Comment 70) A few comments requested clarification of the difference between equipment that is "similar but not identical," proposed as a changes-being-effected-in-30-days supplement, and the SUPAC terminology of equipment of the "same design and operating principle," which is already defined in the SUPAC guidances and the June 1999 proposal as an annual report change. The comment said that the difference is not readily apparent and may lead to varying interpretations of regulatory submission requirements. The comments said that for equipment changes that are of different operating principle and design, FDA should consider the major change category, and for equipment changes that are of the same operating principle but different design, FDA should consider the moderate change category.

FDA agrees and has clarified the requirement by replacing the phrase "of similar, but not identical, design and operating principle that" with the phrase "that of a different design that." Equipment of a different design may or may not have a different operating principle.

(Comment 71) One comment suggested inserting the word "adversely" before "affect" to read: "Replacement of equipment with that of similar, but not identical, design and operating principle that does not adversely affect the process methodology or process operating parameters." The comment said that replacement of equipment that does not adversely affect the process methodology or operating parameters and/or positively affects process methodology or operating parameters should be reported as a minor change.

FDA declines to revise the provision as requested. New § 314.70(c)(1) already states that the changes that should be filed in changes-being-effected supplements are those that have a moderate potential to have an "adverse effect." Adding the word "adversely" to this provision is redundant.

Proposed § 314.70(c)(4) stated that pending approval of the supplement by FDA, except as provided in paragraph (c)(6), distribution of the product made using the change may begin not less than 30 days after receipt of the supplement by FDA. The information listed in § 314.70(b)(3)(i) through (b)(3)(viii) must be contained in the supplement.

(Comment 72) One comment said that the last sentence in § 314.70(c)(4) should be revised to read: "The information listed in paragraphs (b)(3)(i) through (b)(3)(vii) * * *" because currently CGMP validation information, including a reference to appropriate SOPs, is required to be submitted in applications only as it pertains to sterilization processes.

FDA has revised § 314.70(c)(4) to make it consistent with the changes made in § 314.70(b)(3) to address the concerns raised by the comment (see discussion in comment numbers 50 through 54 in section III.C of this document) and also to clarify the term "product."

(Comment 73) One comment said that a time line and dispute resolution process needs to be defined by regulation or guidance in case of disputes regarding the type of information needed to support a change.

FDA does not believe it is necessary to revise proposed § 314.70 to address this issue. Actions by reviewers or other Center officials may be appealed through the appeals mechanism already in place in each Center to the Center Director and, ultimately, to the Commissioner of Food and Drugs. Dispute resolution procedures are detailed in 21 CFR 10.75 and 21 CFR 312.48, and §§ 314.103 and 601.12(h). FDA has also provided additional information in guidance documents. In the **Federal Register** of March 7, 2000 (65 FR 12019), FDA issued a guidance entitled "Formal Dispute Resolution; Appeals Above the Division Level." The guidance describes the mechanism for resolution of procedural (including administrative) and scientific disputes in CDER and CBER.

Proposed § 314.70(c)(5) stated that the applicant must not distribute the product made using the change if, within 30 days following FDA's receipt of the supplement, FDA informs the applicant that either: (1) The change requires approval prior to distribution of the product in accordance with paragraph (b); or (2) any of the information required under § 314.70(c)(4) is missing. The applicant must not distribute the product made using the change until FDA determines that compliance is achieved.

(Comment 74) One comment said that if FDA determines within 30 days of receipt of the supplement that the change is properly submitted but the required information is incomplete, the applicant would be required to supply the missing information and wait until FDA determines that the supplement is in compliance before distributing the product. The comment contended that as long as the firm submits the data requested by FDA, it should be able to go to market and not wait until FDA determines that the supplement is "in compliance," which could take months since FDA is not now bound by the 30-day requirement.

FDA agrees and has clarified the requirement based on this comment. FDA has revised § 314.70(c)(5) to provide that, in the case of missing information, the applicant must not distribute the drug product until the supplement has been amended to provide the missing information.

(Comment 75) One comment asked, when additional information is provided, whether FDA's determination of compliance with the requirements of this section is equivalent to an approval of the supplement.

FDA has revised this section, and this comment is no longer applicable. However, FDA clarifies that it sends a formal letter to an applicant stating that a particular supplement is approved and that no other communication from FDA should be construed as an approval.

Proposed § 314.70(c)(7) stated that if the agency disapproves the supplemental application, it may order the manufacturer to cease distribution of the drug products made with the manufacturing change.

(Comment 76) A few comments recommended that FDA replace this requirement with the following: "If FDA later determines that the supplemental application is not immediately approvable, the agency will work with the applicant to resolve all issues and to assure the continued availability of the drug." Another comment recommended that this requirement be limited to only those cases where an adverse effect on safety or efficacy can be demonstrated. One comment said that although this is the language contained in section 506A(d)(3)(B)(iii) of the act, it is a reversal of long-time FDA policy of allowing firms to respond to deficiencies and get the supplement approved without interfering with distribution. The comment said that FDA should continue its long-standing policy.

FDA declines to revise the provision as requested. The regulation is consistent with section 506A(d)(3)(B)(iii) of the act. There may be some instances where FDA determines, after the drug product made using the change has been distributed, that the information submitted in the supplement fails to adequately demonstrate the continued safety and

effectiveness of the drug product. In such cases, FDA will make all possible efforts to resolve problems with the applicant concerning the supplement submission without requiring the removal of the drug product from the marketplace. In cases where FDA determines that there may be a danger to public health due to continued marketing of the drug product or when FDA determines that the issues may not otherwise be resolved, the agency may require that the applicant cease distribution of the drug product made using the change or that the product be removed from distribution pending resolution of the issues related to the change.

(Comment 77) One comment said that if FDA disapproves a changes-being-effected-in-30-days supplement, the sponsor should be notified within 30 days of this submission as stated in § 314.70(c)(5)(ii).

FDA declines to revise the regulation based on this comment. FDA intends during the 30-day period to focus its review on determining whether the applicant reported the change using the appropriate mechanism and, if so, whether any of the required information is missing. FDA intends to perform the substantive review of the submission as expeditiously as possible, but this is unlikely to occur within 30 days of receipt of the supplement.

F. Changes For Which Distribution of the Drug Product Involved May Commence When FDA Receives a Supplement (Moderate Changes)

Proposed § 314.70(c)(6) stated that FDA may designate a category of changes for which the holder of an approved application making such a change may begin distribution of the drug upon receipt by FDA of a supplemental application for the change. These changes include, under § 314.70(c)(6)(i), an addition to a specification or changes in the methods or controls to provide increased assurance that the drug will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess.

(Comment 78) Several comments recommended that an addition to a specification or change in the methods or controls to provide increased assurance that the drug will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess should be considered to have a minimal potential to have an adverse effect and should be allowed to be filed in the annual report.

FDA declines to revise the regulation as requested. FDA has identified certain specific changes that provide increased assurance that may be submitted in an annual report, such as the tightening of an acceptance criterion. However, this is a general provision and the assessment of whether or not a change provides "increased assurance" is subjective and must be supported by studies and data, as appropriate. FDA must have the opportunity to concur with an applicant's assessment that a change provides "increased assurance" in a timely manner. Reporting of such changes in an annual report would not afford FDA this opportunity because a change may be in effect for up to a year before FDA would have the opportunity to review the change. Changes that do not necessarily provide increased assurance may be a type of change that must be submitted in a changes-being-effected-in-30-days supplement or a supplement that requires approval prior to distribution of the product made using the change.

(Comment 79) One comment recommended that FDA change "addition to a specification or changes in the methods or controls" to "addition to a specification or changes in the tests, analytical procedures, or acceptance criteria."

FDA declines to revise the regulation as requested. The phrase "methods or controls" is not used by FDA to mean tests, analytical procedures, or acceptance criteria. Methods and controls relate to the manufacturing process.

Proposed § 314.70(c)(6)(ii) included the following category: A change in the size and/or shape of a container for a nonsterile drug product, except for solid dosage forms, without a change in the labeled amount of product or from one container closure system to another.

(Comment 80) A few comments recommended adding "a sterile drug product, or a sterile drug substance" to read "* * * container for a nonsterile drug product, except for solid dosage forms, a sterile drug product, or a sterile drug substance without a change." The comments said that changes in the size and shape of containers for sterile drug substances or sterile drug products have only moderate potential impact. The comments said that this is especially true when the nature of the size/shape changes are very minor, as is often the case when suppliers make minute adjustments in their packaging components.

FDA declines to revise the regulation as requested. As discussed in the comments for § 314.70(b)(2)(iii) in section III.C of this document, sterility of drug products or drug substances is a fundamental and essential quality attribute of these drugs and is a critical aspect of the safety assessment. Changes in the container closure system, even if minimal, may affect the sterility assurance of the drug product and are a major change. For sterile drug substances, the effect of changes in the size and/or shape of the container closure system is considered by FDA to be of lower risk because of the differences in procedures for sterilizing drug substances and drug products, but the risk is still higher than for nonsterile products. Therefore, FDA declines to specify in the regulations that these changes can be submitted in a changes-being-effected supplement. Additional information on changing container closure systems for sterile drug substances or drug products is included in the guidance "Changes to an Approved NDA or ANDA."

(Comment 81) Several comments pertained to the phrase "without a change in the labeled amount of product." The comments said that proportional changes (i.e., ratio of the amount of drug product to size of container) are not expected to adversely affect the drug product, and one of these comments recommended that FDA should add "and a change in the labeled amount of product as long as the size of the container/closure system is changed proportionally." Other comments said that a corresponding change in fill quantity, along with a change in container size, is expected and readily acceptable and that it is illogical to assume that a change in the amount of product would present any greater risk than a change in container size.

FDA declines to revise the regulation as requested or with similar language included in § 314.70(d)(2)(iv). The phrase "labeled amount of product" refers to the total quantity of drug product (e.g., milliliters, grams). FDA has included the phrase "without a change in the labeled amount of product" because of the agency's concern about the proliferation of unit-of-use containers that may invite the misuse of drug products. A unit-of-use container is one that contains a specific quantity of a drug product and that is intended to be dispensed to the patient without further modification except for the addition of appropriate labeling. Although few in number, some drug products may cause life-threatening side effects, such as permanent liver damage, if used for longer periods of time than recommended in the labeling. Similarly, certain drugs must be used for a specific length of time (e.g., antibiotics) or the treatment may be ineffective. Unit-of-

use containers that contain a quantity of drug product that invite underuse or overuse of the product as recommended in the labeling may be a public health risk. FDA considers changes in the labeled amount of a nonsterile drug product in a unit-of-use container to have a moderate potential to adversely affect the safety and efficacy of the drug product and expects that these changes would normally be submitted in a changes-being-effected-in-30-days supplement under § 314.70(c)(2)(i). This would give FDA an opportunity to raise a concern about a package presentation prior to distribution of the product.

FDA's concern is less when the "labeled amount of product" is changed in multiple-unit containers for nonsterile drug products. FDA considers this change to have the same level of risk as a change in the size and/or shape of the container. A multiple-unit container is a container that permits withdrawal of successive portions of the contents without changing the strength, quality, or purity of the remaining portion. This type of container is not for direct distribution to patients, but is used by health care practitioners who dispense the drug in smaller amounts in accordance with a physician's instructions. While FDA declines to revise the regulations to specify the distinction between unit-of-use and multiple-use containers because of the complexity of the issue, FDA will address this issue when revising the guidances "Changes to an Approved NDA or ANDA" and "Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products."

Proposed § 314.70(c)(6)(iii)(C) included as a moderate change a change in the labeling to add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the product.

(Comment 82) One comment said that FDA should replace the words "and administration" in § 314.70(c)(6)(iii)(C) with the words "administration and storage."

FDA declines to revise the regulation as requested. The addition or strengthening of a storage statement could reflect a change in the expected characteristics or quality of a drug product and would be a major change. Also, one of FDA's objectives is to have the same drug products stored similarly to avoid confusion in the marketplace. FDA would need to review the proposed change prior to implementation to determine if: (1) The change is appropriate, (2) any changes in product quality causing the labeling change significantly impact the safety or effectiveness of the drug, and (3) there are other issues that need to be addressed either on an individual company basis or globally.

Proposed § 314.70(c)(6)(iii)(E) included as a moderate change any other change specifically requested by FDA.

(Comment 83) One comment said that any changes made to the labeling that are specifically required by the FDA should be reportable in the annual report.

FDA declines to revise the June 1999 proposal as requested but has revised § 314.70(c)(6)(iii)(E) to provide clarification. As stated in the June 1999 proposal, FDA proposed adding this section to allow labeling changes that normally require prior approval to be submitted in a changes-being-effected supplement when FDA specifically requests the change. FDA has clarified § 314.70(c)(6)(iii)(E) as follows: "Any labeling change normally requiring a supplement submission and approval prior to distribution of the drug product that FDA specifically requests be submitted under this provision." FDA has also clarified § 601.12(f)(2)(i)(E) as follows: "Any labeling change normally requiring a supplement submission and approval prior to distribution of the product that FDA specifically requests be submitted under this provision."

G. Changes To Be Described in the Next Annual Report (Minor Changes)

Proposed § 314.70(d)(1) required that changes in the product, production process, quality controls, equipment, or facilities that have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product must be documented by the applicant in the next annual report in accordance with § 314.81(b)(2).

Proposed § 314.70(d)(2)(i) required the following change to be documented in the next annual report: Any change made to comply with an official compendium that is consistent with FDA requirements and provides increased assurance that the drug will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess.

FDA received 18 comments on this provision. Fifteen comments requested that FDA change this requirement to read "Any change to comply with an official compendium;" two comments requested that FDA change this requirement to read "Any change made to comply with an official compendium that is consistent with FDA requirements;" and one comment did not provide a suggested revision.

FDA declines to revise the provision as requested in the comments but has revised the provision to provide further clarification. The basis for this decision is discussed below. The majority of the comments pertained to drugs regulated under, and the statutory requirements regarding official compendia included in, the act. Therefore, FDA has responded to the comments from this perspective. FDA has made corresponding changes to § 601.12(c) and (d) for biologics regulated under section 351 of the PHS Act.

(Comment 84) Many comments said that the proposal to require supplemental applications for some changes that are made to comply with an official compendium fails to recognize the legal status of the USP/NF under the act and undermines the authority of the USP/NF as official compendia and sources of standards. One comment stated that if a drug product meets compendial requirements, it is considered unadulterated under the act. Another comment stated that the USP is the responsible compendial body for regulatory specifications.

Under section 501(b) of the act (21 U.S.C. 351(b)), a drug that is recognized in an official compendium may be considered adulterated if its strength differs from, or its quality or purity fall below, the standards set in the compendium. Determinations of adulteration under this provision of the act must be made in accordance with the analytical procedures set in the compendium. When there is no analytical procedure prescribed in the compendium or the tests prescribed in the compendium are insufficient, the agency can follow the process outlined in the statute and issue a regulation to provide an appropriate analytical procedure. As stated in the act, no drug defined in an official compendium will be considered adulterated under section 501(b) of the act because its strength differs from, or its quality or purity fall below, the standards set in the compendium if the differences from the standard are stated in its label. Under section 502(g) of the act (21 U.S.C. 352), a drug that is recognized in an official compendium may be considered misbranded if the drug is not packaged and labeled as prescribed in the compendium.

The agency is aware of the legal status of the USP/NF under the act as a standard for determining whether a drug may be considered adulterated or misbranded. A compendial product that fails to comply with USP/NF standards

may be considered to be adulterated or misbranded under the act. However, a compendial product can still be considered adulterated or misbranded under other provisions of sections 501 or 502 of the act, even if it complies with USP/NF standards.

While the standards in the USP/NF are legally enforceable standards for determining whether a product is considered adulterated under section 501 of the act, these standards are not considered the complete regulatory specification. The agency is responsible for establishing regulatory specifications as part of the approval of an application. Under sections 505(b) and 505(j) of the act (21 U.S.C. 355(b) and 355(j)) , an application must include a full description of the methods used in and the facilities and controls used for, the manufacture, processing, and packing of the drug. If the specifications included in the description are considered inadequate to ensure and preserve the identity, strength, quality, purity, or potency of the drug, the agency will refuse to approve the application. Standards established by an official compendium may be inadequate for the purposes of approving an application under section 505 of the act. The USP acknowledges that:

> While one of the primary objectives of the Pharmacopeia is to assure the user of official articles of their identity, strength, quality, and purity, it is manifestly impossible to include in each monograph a test for every impurity, contaminant, or adulterant that might be present, including microbial contamination. These may arise from a change in the sources of the material or from a change in the processing, or may be introduced from extraneous sources. Tests suitable for detecting such occurrences, their presence of which is inconsistent with applicable good manufacturing practice or good pharmaceutical practice, should be employed in addition to the tests provided in the individual monograph. (USP 25, General Notices, page 7).

Similarly, while the labeling requirements in the USP/NF are legally enforceable standards for determining whether a product is misbranded under section 502 of the act, use of these standards alone does not ensure compliance with the act. The USP states "articles in this Pharmacopeia are subject to compliance with such labeling requirements as may be promulgated by governmental bodies in addition to the Pharmacopeial requirements set forth for the articles." (USP 25, General Notices, page 12).

Not all compendial standards or changes in existing compendial standards are: (1) Adequate to ensure and preserve the identity, strength, quality, purity, or potency of the drug or (2) consistent with other requirements of the act. For example, a deletion of an impurity test may result in an inadequate standard for ensuring the purity of the drug. Therefore, the agency does not believe that all changes made to comply with an official compendium are of a type that should be reported in an annual report.

(Comment 85) Many comments stated that the phrases "which are consistent with FDA requirements" and "provides increased assurance that the drug will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess" are unclear. Several comments stated that "consistent with FDA requirements" allows for individual review interpretations. Several comments said that deleting or widening a specification due to a change in the USP should be allowed in an annual report.

FDA concurs that the provisions regarding changes to comply with an official compendium should be clarified. Separate discussions of labeling, analytical procedures, and acceptance criteria and test changes follow, along with a discussion of the phrase "consistent with FDA requirements."

Labeling: Under section 502(g) of the act, a drug recognized in an official compendium may be considered misbranded if the drug is not packaged and labeled as prescribed in the compendium. The method of packing may be modified with the consent of the agency. One comment stated that there would be confusion in the marketplace if compendial labeling changes were not instituted uniformly. The agency concurs that all labeling changes made to comply with an official compendium that are consistent with FDA requirements should be reported in an annual report. These changes have minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety and effectiveness of the product. Consistent labeling promotes the safe use of products and reduces confusion in the marketplace.

Analytical procedures: For compendial drugs, the determination of whether the drug is adulterated under section 501(b) of the act must be made in accordance with the analytical procedures set in the compendium except when no analytical procedure is prescribed in the compendium or the tests prescribed in the official compendium are insufficient. In these situations, the agency can follow the process outlined in the statute and issue a regulation to provide an appropriate analytical procedure. Because of the legal status of compendial analytical procedures in the act and other requirements relating to analytical procedures in the statute, the agency concurs that changes in analytical procedures to comply with an official compendium may be filed in an annual report, except for changes to comply with an official compendium that result in the deletion of a test or the relaxation of an acceptance criterion. The agency wishes to emphasize that under FDA's CGMPs, the suitability of all analytical procedures, including compendial procedures, must be verified under actual conditions of use. For example, an assay analytical procedure where degradation products, impurities, or excipients interfere with the analysis is not considered an acceptable analytical procedure. The use of unacceptable analytical procedures, even if specified in an official compendium, can be considered a violation of the act. The agency also wishes to emphasize that a change from an approved analytical procedure that is capable of quantifying impurities to a compendial analytical procedure that cannot quantify impurities is in essence a deletion of an impurities test. This change of procedure should not be reported in an annual report, but should be reported as any other request for deletion of an approved test.

Tests and acceptance criteria: Under sections 505(b) and 505(j) of the act, an application must include a full description of the methods used in and the facilities and controls used for, the manufacture, processing, and packing of the drug. If the specifications included in the description are considered inadequate to ensure and preserve the identity, strength, quality, purity, or potency of the drug, the agency will refuse to approve the application. As previously discussed in this document, the standards established by an official compendium may be inadequate for approving an application under section 505 of the act.

As part of the detailed application review process and in accordance with section 505 of the act, FDA requires that the application include tests and acceptance criteria that the agency believes are necessary to ensure and preserve the identity, strength, quality, purity, and potency of the product. The specifications included in the application are legally binding upon the applicant, and a product that fails to comply with the specifications included in the application can be considered an unapproved drug under section 505 of the act. Compendial standards are often

used in evaluating the specifications proposed in the application. However, compendial standards must often be supplemented with additional tests, such as a specific test for impurities, to ensure the identity, strength, quality, purity, and potency of the drug. Also, the tests and acceptance criteria in an application are often approved without benefit of a compendial standard for a drug because no compendial standard has been established. Situations could arise where, for example, FDA requires tests and acceptance criteria for specific impurities as part of approval of an application. These impurities are not specified in an existing monograph or are not included in a monograph published subsequent to the approval of the drug. If FDA allowed all changes to comply with an official compendium to be included in an annual report, the applicant could interpret this provision as allowing them to delete the tests which were required as a condition of approving the application.

A change to relax an acceptance criterion or delete a test is considered a major change. The agency needs to review a request for this type of change in the context of a particular NDA or ANDA to determine if the change will adversely affect the identity, strength, quality, purity, or potency of the product. Changes such as these, when requested solely at the initiative of the applicant, must be filed in a prior approval supplement. Reporting these changes in an annual report is not appropriate. However, when a change to relax an acceptance criterion or delete a test is made to comply with a change to an official compendium, the change is considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety and effectiveness of the product. The change is considered moderate because: (1) The change has been reviewed by an independent group that has the goal of promoting public health and (2) the agency has had the opportunity through the USP process of reviewing the proposed change in general, but not necessarily in the context of each individual application affected by the change. Based on these factors, the agency will require a changes-being-effected-in-30-days supplement for a change to relax an acceptance criterion or delete a test to comply with a change to an official compendium. A change made to comply with an official compendium that results in a tightening of an approved acceptance criterion or an addition of a test is considered a minor change and may be filed in an annual report.

(Comment 86) FDA proposed that changes to comply with an official compendium could be reported in an annual report only if they were consistent with FDA requirements. Several comments stated that "consistent with FDA requirements" allows for individual review interpretations.

FDA declines to delete this phrasing but wishes to clarify that the term requirements means the requirements of the act or the applicable provisions in the Code of Federal Regulations (CFR). An annual report or changes-being-effected-in-30-days supplement should not be used to implement a change to comply with an official compendium when that change is not consistent with other FDA statutory or regulatory requirements. An example of this is a change to a compendial analytical procedure, when a different analytical procedure is specified in the regulations (e.g., 21 CFR part 610) because the use of the compendial analytical procedure is not consistent with FDA regulations. Another example of this is a change to a compendial analytical procedure that is proven not to be suitable under actual conditions of use because the use of such an analytical procedure, even if specified in an official compendium, is not consistent with CGMPs (21 CFR 211.194). If situations like this occur, applicants should contact the agency, inform them of the situation, and request advice.

For the reason discussed previously in this document, the agency is adding §§ 314.70(c)(2)(iii) and 601.12(c)(2)(iv) to require a changes-being-effected-in-30-days supplement for a relaxation of an acceptance criterion or deletion of a test to comply with an official compendium that is consistent with FDA statutory and regulatory requirements. The agency is revising § 314.70(d)(2)(i) as follows: "Any change made to comply with an official compendium, except a change described in paragraph (c)(2)(iii) of this section, that is consistent with FDA statutory and regulatory requirements." The agency is also revising § 601.12(d)(2)(i) as follows: "Any change made to comply with an official compendium, except a change described in paragraph (c)(2)(iv) of this section, that is consistent with FDA statutory and regulatory requirements."

(Comment 87) Several comments stated that a drug must comply with the compendial quality standards or it may be considered adulterated or misbranded. The comments went on to say that when the USP makes a change and a company cannot comply until FDA approves the change, the marketed drug in the intervening period technically may be misbranded or adulterated if it fails to meet the changed compendial requirements.

The agency wishes to clarify as part of this final rule the circumstances under which a supplemental application must be submitted for changes to comply with an official compendium. A supplemental application must be submitted only when the change involves a relaxation of an acceptance criterion or deletion of a test. The standards for the drug will differ from the standards prescribed in the official compendium until the agency approves the change. However, under these circumstances, the drug as marketed will have tighter specifications or more testing will be performed than has been specified in the official compendium. Therefore, the drug will not fall below the standards set in the official compendium and would not be considered adulterated under section 501(b) of the act.

(Comment 88) One comment said that the proposed language implies that there may be separate and/or different requirements to fulfill USP and FDA criteria. Other comments said that the same product, from different applicants, should be held to the same standards.

As discussed previously in this document, while the specifications in an official compendium are legally enforceable standards under section 502(b) of the act for determining whether a product is considered adulterated, these standards may not be sufficient to ensure and preserve the identity, strength, quality, purity, and potency of the drug as required under section 505 of the act for approval to market a drug. Generally, FDA uses compendial standards in evaluating the specifications proposed in an application. However, compendial standards must often be supplemented with additional tests to ensure the identity, strength, quality, purity, or potency of the drug. Similarly, while the labeling requirements in USP/NF are legally enforceable standards for determining whether a product is misbranded under section 502(g) of the act, use of these standards alone does not ensure compliance with the act. The statutory requirements regarding compendial standards as well as other statutory requirements must be considered to ensure compliance with the act.

The requirements under sections 501(b) and 502(g) of the act for determining whether a product is adulterated or misbranded and of

section 505 of the act for approving an application are applied consistently to all products. Under sections 505(b) and 505(j) of the act, the specifications included in the application must be considered adequate to ensure and preserve the identity, strength, quality, purity, and potency of the drug or else the agency must refuse to approve the application. However, this does not mean that the specifications approved in different applications for the same drug are identical. For example, different analytical procedures may be approved as long as the analytical procedures are appropriate and valid. Another example is that where solvents are used, the agency routinely and consistently requests tests and acceptance criteria for residual solvents. However, because different manufacturers use different solvents, the tests and acceptance criteria will vary depending on the solvents used. In all cases, the approved specifications will have been determined by the agency to be adequate to ensure and preserve the identity, strength, quality, purity, and potency of the drug.

(Comment 89) Many comments stated that FDA is involved in the USP revision process and should use this process to resolve any differences between compendial requirements and FDA requirements and ensure that compendial changes do not compromise safety and efficacy. Once this is accomplished, all changes to comply with a compendial change should be submitted in an annual report.

The USP process for developing or changing a monograph, general notice, or general chapter is an open process. Anyone who is interested in a particular issue has the opportunity to comment. FDA participates in many USP activities, including joint committees and public forums, and has designated persons throughout the agency to act as liaisons to the USP.

FDA recognizes that public standards such as those instituted by the USP are beneficial. However, the USP is a nongovernmental organization that works independently from FDA, and FDA has no authority to stop USP from implementing a new or revised standard. FDA must ensure the identity, strength, quality, purity, and potency of drugs by requiring appropriate specifications. Compendial standards are not always sufficient to provide this assurance. Moreover, certain changes in a public standard, such as deletion of a test or relaxation of an acceptance criterion, cannot always be considered an improvement in the standard, nor is it always clear that the change will not lessen the assurance of the identity, strength, quality, purity, or potency of the products affected by the change. After review of a change such as these in the context of a specific NDA or ANDA, FDA may confirm that the change does not adversely affect the drug. However, allowing such a change to be documented in an annual report would not provide the opportunity for the agency to assess the effect of the change in a timely manner. FDA considers the provisions in the final rule necessary to ensure the safety and effectiveness of drugs.

(Comment 90) Several comments said that the proposed provision regarding changes to comply with an official compendium was inconsistent with the intent of the Modernization Act.

FDA disagrees with these comments. Section 506A of the act requires a change in the specifications in the approved application to be submitted in a supplemental application and approved by the agency prior to the applicant distributing the product affected by the change (section 506A(c)(2)(A) of the act). The act does not distinguish between changes in compendial and noncompendial specifications. The act allows the Secretary to exempt by regulation or guidance the requirement that changes in specifications may be submitted in prior approval supplements. However, the act also requires the agency to establish the reporting category for a change based on the potential for the change to adversely affect the identity, strength, quality, purity, and potency of the drug as they may relate to the safety and effectiveness of the drug. The agency believes the provisions in the final rule regarding changes to comply with changes in an official compendium are consistent with the intent of the Modernization Act.

(Comment 91) One comment also said that the proposal was not consistent with the initiatives under the National Partnership for Reinventing Government (REGO), the National Technology Transfer and Advancement Act (the NTTAA) of 1995 and the Paperwork Reduction Act of 1995 (the PRA).

FDA disagrees with this comment. The comment states that one of FDA's goals under REGO is a more efficient drug development process and review process that will lower the development costs and reduce by an average of 1 year the time required to bring important new drugs to the American people. This REGO goal relates to initiatives for drugs prior to approval by FDA and is not pertinent to this rule. However, one REGO initiative was to reduce the number of manufacturing changes that require agency preapproval for biological products and FDA revised its regulations to achieve this goal (see the **Federal Register** of January 29, 1996 (61 FR 2739), and July 24, 1997 (62 FR 39890)). FDA supports the REGO objective to transform FDA into a customer-oriented, results-driven organization and believes that the final rule, which reduces regulatory burden with respect to postapproval changes for both biological products and human drugs, achieves this objective.

The National Technology Transfer Act of 1995 (NTTAA) (Public Law 104–113, 15 U.S.C. 3701 (1996)) encourages the use of voluntary consensus standards by Federal agencies as a means to carry out policy objectives and puts into law the policies of OMB Circular A–119 (see the **Federal Register** of February 19, 1998 (63 FR 8546)). The standards set by USP/NF are not voluntary standards because the standards are recognized in sections 501 and 502 of the act for the purposes of determining if a compendial drug is adulterated or misbranded. Therefore, the NTTAA is not pertinent. FDA is authorized to cooperate with associations and scientific societies in the revision of the USP (21 U.S.C. 377). FDA is a committed participant in this endeavor and in developing other voluntary and nonvoluntary consensus standards.

The purposes of the PRA (44 U.S.C. 3501–3520) include minimizing paperwork for business resulting in collection of information for the government, ensuring the greatest public benefit from the information collected, and minimizing the cost to the government of the collection of information. Section 506A(b) of the act states that a drug made with a manufacturing change (whether a major manufacturing change or otherwise) may be distributed only if, before distribution of the drug as so made, the holder involved validates the effect of the change on the identity, strength, quality, purity, and potency of the drug as these factors may relate to the safety and effectiveness of the drug. Moreover, each supplemental application or annual report must contain such information as the Secretary determines to be appropriate and include the information developed by the applicant to validate the effects of the change (sections 506A(c)(1), (d)(2)(A), and (d)(3)(A) of the act). The information that will be submitted to support a change is independent of the reporting category for the change. FDA will require the same type of information to be submitted to support a change in a compendial specification regardless of whether the change is reported in a supplemental application or annual

report. There is no additional paperwork burden based solely on the designation of a reporting category for a particular change.

(Comment 92) Many comments said that requiring compendial changes to be reported in anything other than an annual report was an increase in regulatory burden over what has been done in the past. Several comments said that there has been no public discussion about any concerns with the previous policy to allow changes to comply with compendial changes to be filed in an annual report.

FDA recognizes that there has been confusion about the provision in previous § 314.70(d)(1) that allowed any change made to comply with an official compendium to be reported in an annual report. In the **Federal Register** of June 4, 1986 (51 FR 20310), FDA published a proposed rule to clarify and limit the types of compendial changes that could be made in an annual report. FDA was preparing to issue a final rule regarding this proposal when Congress initiated discussions about postapproval manufacturing changes. FDA delayed publishing the final rule and incorporated revisions regarding reporting of changes to comply with an official compendium into its proposed rule implementing section 506A of the act. The provisions in the final rule for changes made to comply with an official compendium might be viewed by some as an increase in burden over how FDA has been interpreting this regulation in the past. However, FDA believes that the provisions are necessary and consistent with the requirements of section 506A of the act to establish a reporting category for a change based on the potential for the change to adversely affect the identity, strength, quality, purity, or potency of the drug product as they may relate to the safety and effectiveness of the drug product. As explained previously, the information that will be submitted to support a change is independent of the reporting category for the change. FDA will require the same type of information to be submitted to support a change in a compendial specification regardless of whether the change is reported in a supplemental application or annual report. There is no additional paperwork burden based solely on the designation of a reporting category for a particular change.

(Comment 93) One comment stated that changes made to comply with changes in an official compendium should not have to include all the information needed for noncompendial products. The comment went on to say that a full description of the test methods and limits should not be necessary and that the company should not have to submit data demonstrating the suitability of a compendial change for the drug product if the compendial change is for a test method change or other change not specifically affecting the quality or the morphology of the material in question.

As previously discussed in this document, under section 506A of the act, each supplemental application or annual report must contain the information that the agency has determined to be appropriate and must include the information developed by the applicant to validate the effects of the change. Guidance on the information that should be submitted to support compendial and noncompendial analytical procedures is available from FDA.

Under proposed § 314.70(d)(2)(ii), the following change was to be documented in the next annual report: The deletion or reduction of an ingredient intended to affect only the color of the product.

(Comment 94) One comment recommended changing the requirement to read "the deletion, reduction or replacement with a color previously used in other CDER/CBER approved products."

FDA declines to revise the regulation as requested. FDA believes that any recommendations it may make concerning notification in an annual report of changes involving replacement of colors are best handled in guidance documents so that the issues and conditions associated with such changes can be fully explained.

(Comment 95) One comment said that changes in formulation, regardless of the intended purpose of the ingredient, are more appropriately addressed in terms of percent change allowed at each level as delineated in the SUPAC guidances.

FDA agrees that the issues relating to changes in components and composition for specific dosage form drug products are better handled in guidance documents, where they can be discussed in detail, rather than in the regulations. FDA included this specific provision in the proposed regulations because this annual report change, with minor editing changes, has been in the regulation since 1985.

Under proposed § 314.70(d)(2)(iii), the following change was to be documented in the next annual report: Replacement of equipment with that of the same design and operating principles except for equipment used with a natural protein product, a recombinant DNA-derived protein/polypeptide product, or a complex or conjugate of a drug with a monoclonal antibody.

(Comment 96) Several comments suggested that FDA delete all words after "principles" to read: "Replacement of equipment with that of the same design and operating principles." One comment said that it is reasonable to report in an annual report replacement with equipment of the same design and operating principles for these (i.e., protein) products.

FDA declines to revise the regulation as requested but has revised it to provide clarity. As discussed in section III.D of this document in response to comments on "Changes Requiring Supplement Submission at Least 30 Days Prior to Distribution of the Drug Product Made Using the Change (Moderate Change)," changes to identical equipment used in the production of proteins could be reported in an annual report. However, a change to equipment of the same design and operating principle, but not identical equipment (e.g., capacity), is not considered a minor change for protein products.

FDA has revised § 314.70(d)(2)(iii) as follows: "Replacement of equipment with that of the same design and operating principles except those equipment changes described in paragraph (c) of this section."

(Comment 97) One comment said the replacement of equipment of the same design and operating principles should not have to be reported. The comment said that for consistency with the existing SUPAC guidances, only a SUPAC subclass (i.e., design) change should be reported.

FDA declines to revise the regulation as requested. FDA's requirement to report changes in equipment of the same design and operating principle in an annual report is consistent with the existing SUPAC guidances. In the future, FDA may issue guidance lessening the reporting requirements in this area for specific cases. However, because of the diversity of drug products and manufacturing processes regulated, FDA is unable at this time to lower the requirements as suggested in the comments.

Under proposed §§ 314.70(d)(2)(iv) and 601.12(d)(2)(v), the following change was to be documented in the next annual report: A change in the size and/or shape of a container containing the same number of dosage units for a nonsterile solid dosage form, without a change from one container closure system to another.

(Comment 98) Several comments said that FDA should delete "containing the same number of dosage units." The comments said that proportional changes (i.e., ratio of the amount of drug

product to size of container) are not expected to adversely affect the drug product, that a corresponding change in fill quantity, along with a change in container size, is expected and readily acceptable, and that it is illogical to assume that a change in the amount of product would present any greater risk than a change in container size.

FDA declines to revise the regulation as requested. As discussed in the response to comment 81 of this document, FDA is concerned about the proliferation of unit-of-use containers that may invite the misuse of drug products.

Under proposed §§ 314.70(d)(2)(v) and 601.12(d)(2)(iv), the following change was to be documented in the next annual report: A change within the container closure system for a nonsterile drug product, based upon a showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium.

(Comment 99) One comment said that the proposal, without further explanation, alters the reporting category applicable to changes within the container/closure system for sterile liquid drugs that are made based on a showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium (for example, the USP). The comment said that under current § 314.70(d)(6), these changes are described in the annual report and do not require FDA prior approval. The comment said that FDA has not provided any rationale for its proposal to require a supplement to be filed in connection with any change within a packaging material for a sterile liquid drug, even in situations in which the change is based on a showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium, and recommended that "nonsterile" be deleted. The comment said that in the same way, it would be unduly burdensome to require FDA prior approval for a change within a container/closure system for a material based on a determination of equivalency made in accordance with a USP monograph that is specifically designed for that purpose. The comment said, for example, the USP chapter for "Polyethylene Terephthalate (PET) Bottles and Polyethylene Terephthalate G (PETG) Bottles" provides standards and tests to characterize PET and PETG bottles "that are interchangeably suitable for packaging liquid oral dosage forms" (USP 25, General Chapter <661> (2002 ed.)). The comment said that FDA is provided with the opportunity to review and comment on USP monographs before they are published in final form; thus, the requirement for an additional FDA prior review of a change made in accordance with USP monograph is unnecessary.

FDA declines to revise the regulation as requested. All container closure systems changes must be supported with data to demonstrate that various characteristics of the drug product and/or container closure system are unchanged or equivalent (e.g., physical, chemical). For a sterile drug product, however, data must also be provided to support that the sterility assurance level and the maintenance of sterility for the product has not been affected. Sterility of drug products is a fundamental and essential quality attribute of these drugs and is a critical aspect of the safety assessment. FDA would consider an assessment of the effects of a change in a container closure system for a sterile product to be inadequate if it did not include tests and data relating to sterility assurance and maintenance of sterility. FDA considers changes in the container closure system for sterile drug products to be changes that may affect the sterility assurance and/or maintenance of sterility of a drug and, therefore, may have significant potential to affect the safety of the drug. Therefore, FDA has identified this change as one that requires prior approval (see comment 34 of this document).

As stated in the June 1999 proposal, this rulemaking sets out broad, general categories of manufacturing changes, and the agency uses guidance documents to provide FDA's current thinking on the specific changes included in those categories. Through guidance, FDA may identify certain container closure system changes for sterile drug products that can be reported other than by submission of a prior approval supplement. Furthermore, an applicant could submit a comparability protocol that would allow it to implement postapproval changes in sterile container closure systems without a prior approval supplement. FDA notes that, as of 2002, no official compendia has finalized an equivalency protocol for container closure systems for sterile drug products. If such a protocol is published in the future, FDA will consider identifying in a guidance a reporting category other than a prior approval supplement for the compendial protocol if the protocol adequately addresses the appropriate scientific issues.

FDA specifically wishes to address the comment's implication that changes made under the USP monograph for "Polyethylene Terephthalate Bottles and Polyethylene Terephthalate G Bottles" could be submitted in an annual report under this provision. As with any change and as required by the act, the applicant must assess the effects of the change on the identity, strength, quality, purity, and potency of the drug product as these factors may relate to the safety and effectiveness of the product. Moreover, USP <661> states that "the suitability of a specific PET or PETG bottle for use in the dispensing of a particular pharmaceutical liquid oral dosage form must be established by appropriate testing." Testing solely by the standards set in this general chapter would not usually be considered by FDA to be sufficient to assess the effects of the change because the interaction between a specific drug product and specific container and closure system should be assessed.

Under proposed §§ 314.70(d)(2)(vi) and 601.12(d)(2)(iii), the following change was to be documented in the next annual report: An extension of an expiration dating period based upon full shelf life data on full production batches obtained from a protocol approved in the application.

(Comment 100) Many comments recommended changes relating to the phrase "full production batches." A few comments recommended deleting the phrase because this requirement would unnecessarily increase regulatory burden, is unnecessarily restrictive, and/or because applicants should be allowed to use either pilot or production batches to extend an expiration date. One comment further said that pilot batches can be used to support the safety and efficacy of the product and for approval of an NDA expiration date; therefore, pilot batches should be allowed to support an extension of an expiration dating period. Another comment recommended that "full" be replaced by "production-scale." The comment said that the word "full" may cause confusion, where batch scale for a product may be varied. The comment said that "full" could be interpreted as that only the largest size batch of an approved batch size range could be used to support an extension of an expiration dating period. One comment said that it should be clarified that the batch need not have been sold. One comment said that production lots should be defined in the "definitions" section to include validation/scale-up batches manufactured by the representative production process within a ten-fold batch size for consistency with SUPAC/BACPAC.

FDA has revised §§ 314.70(d)(2)(vi) and 601.12(d)(2)(iii) by replacing the term "full production batch" with "production batch." FDA declines to include a definition of production batch in the regulations. A definition is included in the ICH guidance entitled "Stability Testing of New Drug Substances and Drug Products." FDA considers a production batch to be one made at production scale using production equipment in a production facility as specified in the application. Production scale does not necessarily mean the largest batch size produced, but a batch of a size or within a batch size range that has been approved in the application. The batch need not have been sold, but should be one that is eligible to be sold (e.g., must pass its specification). In certain cases, FDA allows data from pilot batches to be used to support approval of an application. This is consistent with FDA's efforts to reduce the time it takes to bring new drugs to market. Often there are changes when moving from a pilot manufacturing process to a production process. Although these are usually minor in nature and not expected to affect the stability of the product, the definitive data to support an expiration date should be based on production batches; therefore, FDA declines to revise the regulation to include pilot batches. FDA would expect requests for an extension of an expiration dating period based on data from pilot batches to be submitted in a prior approval supplement.

Under proposed §§ 314.70(d)(2)(vii) and 601.12(d)(2)(vii), the following change is documented in the next annual report: "The addition, deletion, or revision of an alternate analytical procedure that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application." FDA, on its own initiative, is clarifying these sections as follows: "The addition or revision of an alternative analytical procedure that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application, or deletion of an alternative analytical procedure."

Under proposed § 314.70(d)(2)(viii), the following change is to be documented in the next annual report: The addition by embossing, debossing, or engraving of a code imprint to a solid oral dosage form drug product other than a modified release dosage form, or a minor change in an existing code imprint.

(Comment 101) A few comments requested that FDA revise this provision to allow the addition of an ink imprint. One comment further said that under part 206 (21 CFR part 206) (Imprinting of Solid Oral Dosage Form Drug Products For Human Use), which has been in effect for over 5 years, all solid dosage forms are required to have imprints and that the requirement to imprint includes an ink code imprint. Another comment said it is not clear whether the provision includes ink printing, and a cross-reference to part 206 may also be helpful. One comment requested that wording should be added to allow for ink printing on modified dosage forms, as this should not impact drug release.

FDA declines to revise the regulation as requested and is clarifying that inks are not included in this provision. FDA believes that any recommendations on how to report the addition of inks is best handled in guidance documents so that the issues and conditions associated with such changes can be fully explained. For example, FDA would expect that any colors used in an ink imprint would have an acceptable status under FDA regulation (e.g., 21 CFR parts 73 and 74).

(Comment 102) One comment said that FDA should delete the word "minor" from the phrase "minor change" in the code imprint provision (proposed § 314.70(d)(2)(viii)).

FDA declines to revise the provision as requested. The term "minor" has been included in this part of the regulation since 1985. Based on FDA's experience, this wording has not been found to be unclear, nor has it resulted in inconsistent implementation of such changes.

Under proposed § 314.70(d)(2)(x), the following change was to be documented in the next annual report: An editorial or similar minor change in labeling.

(Comment 103) A few comments requested that FDA provide in the regulations specific examples of editorial or similar minor changes in labeling.

FDA declines to provide specific examples in the regulations. As stated in the June 1999 proposal, the agency's approach is to issue regulations that set out broad, general categories of manufacturing changes and use guidance documents to provide FDA's current thinking on the specific changes included in those categories. FDA has provided recommendations on and examples of specific changes in specifications in FDA's guidances entitled "Changes to an Approved NDA or ANDA" and "Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products."

Proposed § 314.70(d)(3)(i) and (d)(3)(ii) required that, for changes described in the annual report, the applicant must submit a list of all products involved, a statement by the holder of the approved application that the effects of the change have been validated, and a full description of the manufacturing and controls changes, including the manufacturing site(s) or area(s) involved.

(Comment 104) Many comments recommended that the term "validated" be replaced with "assessed" or "assessed, as appropriate". The comments' reasoning was similar to that discussed previously in similar comments for § 314.3(b) under section III.A of this document entitled "Definitions."

FDA has replaced the term "validated" with "assessed." However, FDA declines to add the term "as appropriate." Section 506A of the act requires an applicant to assess the effects of each change. FDA believes that the addition of "as appropriate" may incorrectly give the impression that this information is not routinely needed and would result in changes being submitted with insufficient information.

(Comment 105) Concerning the phrase "a list of all products involved," one comment asked whether the same changes, proposed for multiple products, have to be included in this list, and whether FDA wants to be notified as to all of the products that are affected in all annual reports. The comment asked for clarification.

FDA has deleted the phrase "a list of all products involved." FDA does not expect the listing of cross references to drug products approved in other applications. FDA does expect the changes to be described fully (§ 314.70(d)(3)(ii)). If there are multiple products in an application (e.g., strengths), FDA would expect the description to identify which products in the application are affected by the change.

(Comment 106) One comment said including a statement that a change has been validated or assessed presents undue additional burden to the applicant. The comment said that assessment is guaranteed in the filing via provision of relevant supportive data and that restating this fact of compliance with regulatory requirements is redundant.

FDA disagrees that the requirement to include this statement is an undue

additional burden and declines to revise the regulation as requested.

(Comment 107) A few comments said that specifying details of exact "areas involved" is inappropriate, since this information is not typically part of the NDA filing, but is subject to field inspection. The comment said it should not be provided in the annual report.

FDA disagrees that this information is only necessary for field inspections and declines to make the revision. This information may not be essential in all cases. However, it is necessary for many manufacturing site changes. For example, FDA requires the specific filling line/room for sterile products to be identified in the application.

Proposed § 314.70(d)(3)(iii) required that, for changes described in the annual report, the applicant must submit the date each change was made, a cross-reference to relevant validation protocols and/or SOPs, and relevant data from studies and tests performed to evaluate the effect of the change on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product (validation).

(Comment 108) One comment recommended that § 314.70(d)(3)(iii) be deleted entirely because it represents additional reporting requirements that are not consistent with the act.

FDA declines to delete § 314.70(d)(3)(iii). Section 506A(d)(2)(A) of the act requires that an annual report contain such information as FDA determines to be appropriate and the information developed to assess the effects of the change. FDA is specifying the type of information it expects to be included in an annual report, and this action is consistent with the act.

(Comment 109) A few comments recommended that FDA should delete the phrase "the date each change was made." The comments included the following reasons for this recommendation: (1) Specifying an exact implementation date would present an undue burden on both manufacturing and regulatory affairs personnel, (2) the addition of this information to existing practice would result in increased regulatory burden, (3) the requirement is ambiguous as to whether the date is to be the date the product was made with the change or some other date such as the date the product made with the change was put into market distribution, and (4) the data represent information best suited for a field inspection. Some comments stated that the fact that an applicant has reported a change in an annual report covering a specified time period should be sufficient for agency review.

FDA declines to revise the regulation as requested. The date when a change is implemented is important to identify the production batches that may be affected by the change. This is important for various reasons, including allowing reviewers to compare data from different batches prepared at different times to determine if a change has affected product quality. FDA has required the date of implementation for changes reported in annual reports since 1985 under § 314.81(b)(2)(iv)(b) and does not believe that this provision can be construed as an undue or additional burden or the sole purview of a field inspection.

To maintain consistency with § 314.81(b)(2)(iv)(b), FDA has revised the phrase to read: "The date each change was implemented." FDA considers "the date each change was implemented" to be the date that the condition established in the approved application is changed, not when the product made with the change is distributed.

(Comment 110) Many comments said that the phrase "a cross-reference to relevant validation protocols and/or SOP's" should be deleted. The comments included the following reasons for this recommendation: (1) The addition of this information to existing practice would result in increased regulatory burden, (2) the requirement is ambiguous as validation protocols and/or SOPs are needed only in certain situations, and (3) the data represent information best suited for a field inspection.

FDA has revised this provision to clarify when a cross-reference to validation protocols and SOP's are needed. As discussed earlier in this document in response to similar comments on § 314.70(b)(3), validation protocols and data need not be submitted in the application, unless otherwise specified by FDA, but should be retained at the facility and be available for review by FDA at the agency's discretion. For most products, FDA does not require the submission of validation protocols and data. However, for a natural product, a recombinant DNA-derived protein/polypeptide, a complex or conjugate of a drug substance with a monoclonal antibody, or sterilization process, FDA does require the submission of validation protocols for certain critical manufacturing processes unique to these drug substances and drug products. In addition, an applicant is required to submit a "full description of controls used for, the manufacture, processing, and packing of a drug" (section 505 of the act). This information may be submitted in different forms, including SOPs. In most cases, SOPs do not include information relevant to the NDA or ANDA review, but rather information relevant to determining an applicant's compliance with CGMPs. However, in the case of a natural product, a recombinant DNA-derived protein/polypeptide, a complex or conjugate of a drug substance with a monoclonal antibody, or a sterilization process, information contained in SOPs is often relevant to the review of certain aspects of an application.

(Comment 111) A few comments recommended that the term "validation" be deleted. FDA also received comments requesting that the use of the terms drug, drug product, drug substance, and product be standardized.

FDA, on its own initiative, has divided proposed § 314.70(d)(3)(iii) into three paragraphs to provide clarity. FDA has clarified the information originally proposed in § 314.70(d)(3)(iii) by making changes consistent with § 314.70(b)(3)(vi) and (b)(3)(vii) and deleting the term "validation." On its own initiative, FDA is replacing the statement "evaluate the effect of the change on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product (validation)" with "assess the effects of the change" because this phrase is defined in § 314.3(b).

H. Protocols

Proposed § 314.70(e) stated that an applicant may submit one or more protocols describing the specific tests and validation studies and acceptable limits to be achieved to demonstrate the lack of adverse effect for specified types of manufacturing changes on the identity, strength, quality, purity, or potency of the drug as these factors may relate to the safety or effectiveness of the drug. Such protocols, or changes to a protocol, would be submitted as a supplement requiring approval from FDA prior to distribution of a drug produced with the manufacturing change. The supplement, if approved, may subsequently justify a reduced reporting category because of the reduced risk of an adverse effect.

(Comment 112) Many comments recommended that protocols be submitted in changes-being-effected supplements. The reasons for this recommendation included: (1) The expected brevity of the review of the protocol, (2) the proposed change could be implemented and approved in the time it takes for approval and execution of the protocol, and (3) the ability to implement a protocol faster would bring

much needed regulatory relief. One comment said that mandatory limits on protocol review times should be established, otherwise there may be less of an incentive for applicants to adopt this procedure. Another comment said that requiring prior approval for these protocols may be construed as an increase in regulatory burden.

FDA declines to revise the regulation as requested. The time it takes FDA to review information is not a factor in determining how the change should be submitted. However, FDA does expect that it will take a substantial amount of time to review such a protocol. It is expected that applicants will use protocols to justify a reduced reporting category for a particular change. For example, applicants may request that they be allowed to implement a major change without prior approval by FDA. These protocols will in effect reduce regulatory oversight of the specified changes, and FDA considers this reduced oversight to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. Therefore, these protocol submissions are classified as major changes.

Whether or not a proposed change could be implemented and approved in the time it takes for approval and execution of the protocol would be a factor in an applicant's decision to submit a protocol. However, increased efficiency could be achieved overall because a protocol can be used repeatedly for changes within the scope of the protocol. Also, fewer or no deficiencies are expected with a change implemented using a protocol, if properly executed, than with a change for which the specific tests, studies, and acceptance criterion were not discussed with the agency prior to the submission of the information.

FDA continually strives to reduce review times, including the time it takes to approve manufacturing changes. In addition, this rule reduces the overall regulatory burden by allowing many changes to be implemented without prior approval by FDA. As previously discussed in this document, FDA considers a protocol submission to be a major change. Therefore, FDA declines to allow these changes to be submitted in a changes-being-effected supplement to effect faster implementation. FDA also declines to establish mandatory limits on protocol review times. The timing of a review of a supplement for a protocol will be in accordance with current practice for reviewing supplements requiring FDA approval prior to implementation.

FDA does not agree that requiring prior approval for these protocols is an increase in regulatory burden. Where previously allowed by regulations, these changes were specified as requiring prior approval, and this rule just extends that option of submitting protocols for all human drugs. FDA emphasizes that the submission of a protocol is voluntary, and if an applicant decides that submission of a protocol is not beneficial, the applicant can make changes to an approved application by other means specified in the regulations.

(Comment 113) One comment said it would like to operate with the understanding that if a relevant protocol is subsequently published in an official compendium or FDA document, the less burdensome protocol may be applied.

FDA is unable to address this question in a general manner because of the complexity of the issues and the newness of comparability protocols for human drugs. A comparability protocol is an applicant and drug product specific document. Whether a comparability protocol could be superseded would depend on the product and changes covered by a comparability protocol.

(Comment 114) FDA received many comments requesting specific guidance on developing protocols. A few comments recommended that FDA issue a guidance document that includes specific examples of comparability protocols that are approvable. Another comment said that the comparability protocol guidance should contain a sufficient level of detail on testing requirements. One comment said it would welcome FDA's involvement in drafting "common" comparability protocols, so that consistent requirements are imposed on all sponsors. The comment said that, alternatively, FDA guidance on comparability protocol format and content would be helpful.

In the **Federal Register** of February 25, 2003 (68 FR 8772), FDA published a draft guidance on comparability protocols. FDA wishes to advise applicants that while in certain cases FDA may be able to provide specific examples of acceptable protocols or "common" comparability protocols, it is likely that these will be limited because a comparability protocol is an applicant- and drug product-specific document. Applicants will, in most cases, be responsible for developing their own protocols.

(Comment 115) One comment said that, in a manner similar to the procedure developed for disseminating bioequivalence guidance information, comparability protocols that have been reviewed and approved by the agency should be made available under the Freedom of Information Act. The comment said that this practice will help promote harmonization within the agency with respect to postapproval change and may provide interested parties with guidance on the agency's general submission requirements.

After FDA issues an approval letter, data and information in an application will be eligible for public disclosure to the extent permitted by the applicable statutes and agency regulations (see, for example, the Freedom of Information Act (5 U.S.C. 552), the Trade Secrets Act (18 U.S.C. 1905), 21 CFR part 20, and §§ 314.430 and 601.51).

(Comment 116) One comment recommended that FDA encourage the use of packaging equivalency protocols to reduce regulatory reporting burdens, expedite approval of manufacturing changes, and simplify reporting coordination for packaging manufacturers. The comment noted that submission of these protocols was sometimes discouraged by FDA in the past. The comment also suggested that such protocols may be submitted within Type III drug master files (DMFs) to expedite the implementation of manufacturing changes at the packaging and packaging component manufacturer level.

Protocols, including packaging equivalency protocols, may be submitted for FDA consideration. Under certain circumstances, such as changes affecting a large number of applications, FDA may review a protocol submitted to a Type III DMF that will be used to support changes affecting drug product applications. Information in a DMF is not approved or disapproved; therefore, any protocol submitted to a DMF cannot be approved (§ 314.420). Administrative issues relating to review of protocols in a DMF present some unique challenges, and a DMF holder should coordinate with the agency prior to submitting such a protocol.

(Comment 117) One comment requested that the words "validation studies" be clarified. The comment asked whether this means "assessment studies" to assess the impact of the change, or does it refer to CGMP validation studies. The comment said that if it refers to CGMP validation studies, it should only be applicable for sterility validation. A few comments requested that the provision be clarified to state that a protocol can be submitted in an original application.

FDA has clarified the provision by deleting the word "validation" and indicating that a protocol may be submitted in an original application. Various types of studies, including validation studies, may be needed in a protocol. A comparability protocol can be submitted in an original application or after approval of the application in a supplement requiring approval from FDA prior to distribution of a drug product produced with the manufacturing change.

On its own initiative FDA has revised § 314.70(e) by replacing the phrase "acceptance limits" with "acceptance criteria" to promote consistency in the terminology used in the definition of specification and the phrase "purity, or potency" with "purity, and potency" for consistency with section 506A of the act.

I. Implementation of the Final Rule and Guidance

(Comment 118) Several comments urged FDA to withdraw the June 1999 proposal and guidance and develop new documents and permit an opportunity for comment. The comments encouraged FDA to work in collaboration with the industry and the public in crafting improved versions of these documents. The comments contended that the June 1999 proposal and guidance fail to realize the intent of Congress to relieve regulatory burden; that a substantial number of individual issues in the June 1999 proposed rule and guidance require revision; that there was a lack of industry and public involvement in drafting the documents; and, too short a time period was given for comments and subsequent revisions.

FDA declines to withdraw the June 1999 proposal and guidance. FDA's procedures for rulemaking are governed by the Administrative Procedure Act (5 U.S.C. 553) and set forth in FDA regulations at 21 CFR 10.40 and 10.80. Guidances are developed in accordance with the procedures set out in FDA's good guidance practices regulation (see the **Federal Register** of September 19, 2000 (65 FR 56468), and 21 CFR 10.115). As discussed previously in this document, the use of guidance documents will allow FDA to more easily and quickly modify and update important information. Moreover, section 506A of the act explicitly provides FDA the authority to use guidance documents to determine the type of changes that do or do not have a substantial potential to adversely affect the safety or effectiveness of the drug product. In the June 1999 proposal, FDA proposed to implement section 506A of the act for human NDAs and ANDAs and for licensed biological products. In that same issue of the **Federal Register**, FDA announced the availability of a draft guidance for industry entitled "Changes to an Approved NDA or ANDA" to assist applicants in determining how they should report changes to an approved NDA or ANDA under section 506A of the act and under the proposed revisions to the human drug regulations pertaining to supplements and other changes to an approved application. FDA allowed for public participation in the development of the regulation and guidance consistent with FDA regulations and policy and to the extent practicable. The time period to provide public comment was consistent with FDA's regulations and statutory requirements. FDA also held a public meeting on August 19, 1999, to hear comments on the guidance and the proposed rule. In the **Federal Register** of November 23, 1999 (64 FR 65716), FDA announced the availability of a final guidance to assist applicants in determining how they should report changes to an approved NDA or ANDA under section 506A of the act (the November 1999 guidance). FDA has carefully considered the public comments and has revised the regulation and the guidance as appropriate. FDA believes that the final regulation and guidance provide for significant reduction in regulatory burden and therefore fulfill the intent of Congress.

(Comment 119) One comment recommended that FDA publish the final rule as soon as possible to minimize confusion during the transition period when section 506A of the act will govern changes.

FDA has carefully considered the public comments submitted on the June 1999 proposal and has issued a final rule as expeditiously as possible.

(Comment 120) One comment stated that the final rule should be implemented through a "phasing in" of the regulation in order to educate industry and agency reviewers. The comment stated that the final promulgation and implementation of the proposed rule should be undertaken in conjunction with an industry-wide educational effort. The comment said that due to the cost and broad scope of the proposal, seminars or public workshops on the final rule would be of value and would allow for additional input from all affected parties. The comment stated that the impact of the proposed rule will affect regulatory practices and expectations of manufacturers, and by carrying out seminars, FDA could publicize and prepare all concerned for the new requirements. The comment also stated that the public seminars would serve to clarify regulatory expectations and interpretations.

FDA does not believe that phasing-in the regulation is necessary because section 506A has been in effect since November 20, 1999, but does intend to discuss the revised regulation and final guidance in public forums. FDA has already held public forums, such as the American Association of Pharmaceutical Scientists (AAPS)/FDA Workshop on Streamlining the CMC Regulatory Process for NDAs and ANDAs (June 11–13, 2002) to obtain feedback on postapproval changes. FDA will consider the information obtained from this workshop in any future updates of the guidance. FDA does not expect its reviewers to encounter many difficulties in the implementation of this regulation as FDA reviewers have been working with section 506A of the act since it became effective.

(Comment 121) Another comment said that FDA should issue a written explanation or hold a public meeting to discuss the impact of allowing the current statute to expire without a new rule being formally approved. The comment said that FDA should not allow the proposal to be implemented without adequate public comment and review simply because the statute may expire.

The statute has not expired, and FDA assumes that the comment refers to the expiration of § 314.70. Congress mandated that section 506A of the act "takes effect upon the effective date of regulations promulgated by the Secretary of Health and Human Services to implement such amendment, or upon the expiration of the 24-month period beginning on the date of the enactment of this Act, whichever occurs first" (section 116(b) of the Modernization Act). Since November 20, 1999, FDA's regulation of NDA and ANDA postapproval changes has been based on section 506A of the act. The guidance entitled "Changes to an Approved NDA or ANDA" has represented FDA's current thinking on how to apply the requirements of section 506A of the act. FDA has allowed for public participation consistent with applicable regulations and statutes.

(Comment 122) One comment requested that FDA consider "grandfathering" changes already in progress by industry based upon already approved SUPAC guidances. The comment said that its ability to continue to supply product to the marketplace can be adversely affected by now having

to redefine the reporting requirements and extend the time to implementation.

FDA declines to provide for grandfathering of changes already in progress. FDA does not believe that this is necessary. FDA carefully considered the existing SUPAC guidances when developing the regulations and the guidance "Changes to an Approved NDA or ANDA" and does not believe that there will be situations where implementation time will be significantly extended. There may be a limited number of cases where implementation may be delayed for 30 days because of the new reporting category specified in section 506A of the act "Supplement—changes being effected in 30 days," but FDA does not believe this is an undue hardship.

(Comment 123) A comment noted that a number of relevant guidance documents required to support the proposed regulations are not yet implemented (e.g., stability), nor is the guidance "Changes to an Approved NDA or ANDA." The comment recommended that a finite period be established in which these guidance documents be completed and issued. A few comments recommended that all affected guidance documents, such as the SUPAC guidances, be revised expeditiously to minimize confusion regarding conflicting information. One comment recommended related guidances be reviewed within 60 days after issuance of the final rule.

In the **Federal Register** of November 23, 1999, FDA announced the availability of a final version of the guidance for industry entitled "Changes to an Approved NDA or ANDA." This guidance has been revised to conform to this final rule revising § 314.70. FDA continues to update and develop guidances to address particular regulatory and scientific issues. FDA publishes these guidances as expeditiously as possible given its resources and priorities. If guidance for either recommended filing categories and/or information that should be submitted to support a particular postapproval manufacturing change is not available, the appropriate FDA staff can be consulted for advice.

(Comment 124) One comment requested that during the transition period, FDA permit industry to use the guidance document that provides the least burdensome regulatory requirement and the lowest reporting category.

Section 506A of the act and the final regulations provide for a new approach to establishing the reporting category for postapproval changes and for an additional reporting category. To accommodate these changes, FDA has stated that to the extent the recommendations on reporting categories in the guidance "Changes to an Approved NDA or ANDA" are found to be inconsistent with guidance published before the "Changes to an Approved NDA or ANDA" guidance was finalized, the recommended reporting categories in the previously published guidances are superseded.

(Comment 125) One comment noted that the preamble to the June 1999 proposal stated that to the extent that the recommendations on reporting categories in the draft guidance, when finalized, are inconsistent with previously published guidance, such as the SUPAC guidances, the recommended reporting categories in such prior guidance will be superseded by this new guidance upon its publication in final form. The comment said that CDER intends to update the previously published guidances such as SUPAC, to make them consistent with this new guidance. The comment said it wholly supports the creation and use of guidance documents and, in this particular instance, recommends that the SUPAC provisions relating to changes in the qualitative or quantitative formulation of the drug be retained. The comment said that any revisions to current guidance documents should not result in more burdensome requirements.

The recommendations in the SUPAC guidances regarding qualitative and quantitative formulation changes can still be used. FDA intends to revise current documents as appropriate.

J. Comments Specific to Biological Products

(Comment 126) A few comments discussed the need for FDA to issue guidance for the blood banking industry for changes to an approved application. The comments specifically requested clarification on the submission of information pertaining to annual reports, comparability protocols, changes in the site of testing from one facility to another, and equipment upgrades even when a change is due to equipment upgrades that have already received 501(k) clearance. In addition, the comments said that FDA needed to consider the least burdensome mechanism for submitting the various changes.

FDA agrees that guidance for the blood banking industry is needed in this area, and in the **Federal Register** of August 7, 2001 (66 FR 41247), FDA issued the guidance "Guidance for Industry: Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture."

The guidance is intended to assist manufacturers of Whole Blood, Blood Components, Source Plasma, and Source Leukocytes in determining which reporting mechanism is appropriate for a change to an approved license application. Under each section of the guidance, FDA provides categories of changes to be reported under § 601.12. A list of various changes that falls under each category is also provided. The lists are not intended to be all-inclusive. The guidance describes the format for the annual report and further explains the comparability protocol. The guidance also addresses facility and equipment changes.

The 510(k) clearance of a device to be used in a blood bank setting provides assurance that the device is substantially equivalent to a legally marketed device for which premarket approval was not required. For equipment upgrades related to a 510(k) device, the clearance of the device does not address implementation of the device in a specific blood bank setting nor does it address the procedures used by the establishment, the qualification and training of staff operating the equipment, onsite validation of processes, and ongoing process control and quality control. The category for which a change is to be reported depends on the impact of the change upon the specific biological product.

(Comment 127) One comment asked what analysis FDA has performed to determine what types of changes should be reviewed by the agency. For example, in the **Federal Register** of August 3, 1993 (58 FR 41348), FDA, in adding requirements to the labeling CGMP regulations, provided an analysis that labeling errors accounted for an inordinate number of recalls. FDA then issued regulations to address this problem. The comment said, however, that labeling changes are not addressed in CBER's guidance on change control and historically have not been emphasized during review of supplements and other changes to an approved application. The comment asked if CBER has done any systematic, methodical, written review of warning letters, revocations, suspensions, recalls, injunctions, 483-items, and so forth, so that review of supplements is focused on problems that FDA knows are likely to result in public health concerns, regulatory, or legal action.

Prior to the January 29, 1996 (61 FR 2739), proposed revision of § 601.12, FDA performed an informal retrospective review of supplements. It

was the intent of that review to focus the review of manufacturing changes on those with the greatest potential for adverse effect on the products. Labeling changes, although not generally tracked as supplements at that time, were also considered in the review. FDA does not agree with the comment that labeling changes have not been emphasized during review of supplements. Until the publication of the July 24, 1997 final rule (62 FR 39890) (the July 1997 final rule) that revised § 601.12, all labeling changes required approval prior to implementation. The July 1997 final rule allowed certain minor editorial changes to be part of an annual report. Other changes intended to enhance the safety of use of the product could be reported as a changes-being-effected supplement. Substantive changes to labeling still require approval prior to implementation.

(Comment 128) One comment said that in the July 1997 final rule, FDA has asserted that revision of the change-reporting regulations will reduce the burden of reporting changes to the agency. The comment asked whether this is synonymous with reducing the number of reports of changes to the agency. If not, the comment asked what is meant by "reducing the burden:" for example, reduction of the amount of time between submission and approval, or reduction of the amount of data submitted. The comment asked whether FDA has actually analyzed the number of supplements submitted since the original changes to the reporting requirements, and whether the number of supplements has been reduced. The comment asked whether the analysis includes supplements due to labeling changes. The comment noted that FDA allowed for the submission of "comparability protocols." The comment said that once a comparability protocol is reviewed and approved, the change still must be reported, albeit a preapproval supplement may be reduced to a changes-being-effected supplement, and so forth, for each category of change. The comment asked whether FDA has considered these types of submissions in determining if the number of submissions has been reduced and if the total review time for a change has been reduced.

Fewer reports was only part of the reduction of reporting burden mentioned in the July 1997 final rule. The revision of § 601.12 was also intended to allow for more rapid implementation of certain manufacturing changes and to decrease the amount of information required for those changes contained in an annual report. While the comparability protocol was included in the assessment, without experience it was difficult to determine whether it would actually result in decreased reporting or increased efficiency. There is still insufficient experience with these supplements to make a clear determination on that point.

No formal comparison has been made of numbers of supplements received in CBER before and after the revision of § 601.12. Multiple changes to regulatory approaches make a direct comparison very difficult. Labeling changes, while requiring approval, were not tracked as supplements prior to the revision. Consequently, numbers of labeling changes are not readily available through an automated data system. The change to the Biologics License Application from the Product License Application/Establishment License Application approach also has had an effect on the number of submissions to CBER. Further, as the comment points out, there are now more applicants submitting supplements on more products. Even if a comparison of supplement submission numbers were done, the results would be difficult to evaluate.

(Comment 129) One comment said that the June 1999 proposal may perpetuate some existing confusion about the applicability of the regulations set forth in part 600 (21 CFR part 600). Current part 600 does not include the term drug; however, in the definitions section of proposed § 600.3(hh) and (ii), as well as in several other places in the June 1999 proposal, the term "drug" is used rather than biological product. The comment requested that FDA revise the June 1999 proposal to clarify those sections that apply exclusively to biological products, and those that apply to both drugs and biological products.

FDA agrees with the comment. FDA is clarifying the definitions in proposed § 600.3(hh) and (ii) (new § 600.3(jj) and (kk)) by replacing the terms "drug substance(s)" and "drug product(s)" with "product(s)." The term "products" is defined in § 600.3(g). For new drugs, the terms "drug substance(s)" or "drug product(s)" are now used consistently throughout part 314 in this rule.

(Comment 130) One comment said that § 601.12(d)(3)(iii) would require blood establishments to submit a statement that the effects of the change have been validated. The comment said that this is an additional, although minor, increase in the documentation and reporting burden for the blood industry. Because blood establishments are already required to keep validation documentation on file, and blood establishments are inspected on a regular basis, the comment requested that the requirement to submit such a statement be deleted for blood establishments.

FDA disagrees with the comment that blood establishments should be exempt from the requirements of § 601.12(d)(3)(iii). These establishments are already required to report the items listed in § 601.12(d)(3)(i) and (d)(3)(ii). Adding a statement that the effects of the change have been assessed does not add burden beyond the existing requirement and provides valuable information to the agency concerning the establishment's change controls.

(Comment 131) One comment said that the June 1999 proposal would require that a supplement or annual report include in the cover letter a list of all changes contained in the supplement or annual report. The comment said that this new requirement will increase the reporting burden for blood establishments. The comment said that CBER has stated that Form FDA 356h is a cover letter. The comment asked why then must blood establishments fill out this additional new "cover letter." The comment also said that to require blood establishments to reiterate all of the changes that they have compiled and reported in their annual reports in a cover letter accompanying that annual report is duplication of effort. The comment said that the annual report itself is an increase in the reporting burden of blood establishments and was not required before the implementation of the form with its intended paperwork reduction and regulatory efficiency goals. The comment requested that multiple cover letters and the requirement to reiterate all of the changes contained in the report be deleted.

FDA agrees in part with the comment. Proposed § 601.12(a)(5) has been revised to remove the reference to a cover letter for annual reports. The need for a list of the changes contained in the supplement results from the practice of including more than a single change in a supplement. This list is necessary to ensure that all changes are properly identified and addressed in a timely manner. The comment misinterprets statements by CBER on the nature and use of Form FDA 356h. FDA has explained that Form FDA 356h is essentially a cover sheet that provides FDA with information necessary for the identification and administrative processing of a submission. It does not provide detailed information on the content of a submission, such as the number of changes that might be

covered. This necessary information may be conveyed most easily in a simple cover letter that is provided with the supplemental application. It is not FDA's intent that information in the completed Form FDA 356h be duplicated in a cover letter.

(Comment 132) One comment said FDA requires that a field copy of a supplement (except for labeling) be provided to an applicant's local FDA office. As the field inspection force is now routinely involved in the inspection of biologics, the comment asked whether FDA has considered making this a requirement with regard to CBER supplements.

FDA disagrees with the comment. FDA has considered extending the field copy requirement to CBER supplements. The field inspection force is involved in the inspection of biological products through the Team Biologics Initiative. Under this program, a cadre of inspectors has been drawn from field offices throughout FDA. Consequently, it is unlikely that the personnel participating in a given inspection would be assigned to that applicant's home FDA office. FDA does not believe that extending the field copy requirement to CBER supplements has sufficient benefit to the agency to justify the additional paperwork requirements.

(Comment 133) One comment said that the proposal to allow an applicant to request an expedited review of a supplement if a delay in making the change would impose an extraordinary hardship or for public health reasons should be reserved for manufacturing changes made necessary by catastrophic events (for example, fire). These requests should be limited to events that could not be reasonably foreseen and for which the applicant could not plan.

The policy of CBER and CDER has been that applicants requesting expedited review because of catastrophic events should do so only when the event could not be reasonably foreseen. Requests for expedited review will be evaluated on a case-by-case basis and it should be understood that not all requests will be granted.

(Comment 134) One comment noted that the proposal states that if FDA disapproves a supplemental application, FDA may order the manufacturer to cease distribution of the drug products made using the manufacturing change. The comment said that many blood establishments will not even attempt to use this provision because of the possibility of a recall being required by FDA if the manufacturer has misjudged the categorization of the supplement. The comment said that this uncertainty has already resulted in blood establishments pursuing an unnecessarily conservative approach to reporting certain types of changes and, consequently, implementing new technologies slower than necessary. The comment said that to help blood establishments implement process improvements more efficiently, the proposal should be revised to include examples of circumstances under which a cease distribution and subsequent recall would likely be ordered and those under which it would not.

FDA disagrees with the comment about the blood industry's failure to use the provision. The reason for the 30-day delay associated with the changes-being-effected-in-30-days supplement is to allow the agency to notify the applicant before the product is distributed that they have selected the wrong category for the supplement. In the case where the category is correctly chosen but the supplement cannot be approved, the agency will work with the applicant to minimize the impact of that decision. As discussed previously in this document, CBER has published a guidance for the Blood Industry that clarifies what categories changes should fall into and what information should be submitted to decrease the possibility of an error that might result in a recall. As previously mentioned in this document, the availability of the guidance was announced in the **Federal Register** of August 7, 2001 (66 FR 41247).

(Comment 135) One comment noted that the June 1999 proposal states that additions, deletions, or revisions to alternative analytical procedures (that provide the same or increased assurance of the identical strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application) be included in the annual report. The comment said that blood establishments currently are permitted to use § 640.120 to obtain approval for alternate procedures. The comment said that since FDA will already be aware of this change on the date they have granted the approval, such change should not need to be included in blood industry annual reports. The comment said that in keeping with the paperwork reduction principles of the Modernization Act, this section should be revised so reporting of changes already approved under § 640.120 requests is not required in an annual report.

The comment has misinterpreted the concept of an "alternative" analytical procedure (one procedure that can be substituted for another) with the concept of an alternative or an exception to a requirement in the regulations that the applicant views as providing equivalent safety or efficacy. In the case of the latter, the applicant must request approval under § 640.120 before implementing otherwise they will be in violation of the regulatory requirement. An alternative or exception approved under § 640.120 does not have to be included in an annual report.

(Comment 136) One comment concerned proposed § 601.12(f)(2)(i)(E) which provides that labeling changes that normally require a prior approval supplement be submitted in a changes being effected supplement when FDA specifically requests the change. The comment said that industry-wide labeling changes should be categorized as an annual report for blood establishments since uniform labeling requirements already exist, and the blood establishment would simply be reporting that they have adopted the change. In addition, FDA already permits reporting of changes to procedures initiated at the request of FDA to be reported in an annual report. The comment requested that for blood establishments, FDA require that industry-wide labeling changes be reported to FDA in an annual report.

FDA agrees in part with the comment. Many industry-wide labeling changes are initiated by the agency through guidance. If labeling changes include specific language consistent with FDA recommendations, changes to that specific labeling may be reported in the annual report. For example, a majority of the blood industry uses the American Association of Blood Banks circular of information that FDA reviews and recognizes as acceptable before it is printed for use by the blood industry. In this case, FDA does not need to review individual submissions. However, if an establishment uses an individually prepared circular, FDA would want any change to be submitted to FDA, at a minimum, at the time the change is effected because of the impact the change may have on the safe and effective use of a product. Generally, guidance on recommended changes to labeling will include information on how to report the change.

IV. Conforming Amendments

The regulations on supplements and changes to an approved application or license are cited throughout FDA's regulations. Because FDA is revising these regulations, the agency is taking this opportunity to make conforming amendments to 21 CFR parts 5, 206, 250, 314, 600, and 601 to reflect this final rule. These conforming amendments will ensure the accuracy and consistency of the regulations.

V. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Executive Order 12866 classifies a rule as significant if it meets any one of a number of specified conditions, including having an annual effect on the economy of $100 million or adversely affecting in a material way a sector of the economy, competition, or jobs. Under the Regulatory Flexibility Act, if a rule has a significant economic impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of the rule on small entities. Section 202 of the Unfunded Mandates Reform Act requires that agencies prepare a written assessment of anticipated costs and benefits before proposing any rule that may result in an expenditure by State, local, and tribal governments, in the aggregate, or by the private sector of $100 million in any one year (adjusted annually for inflation).

The agency believes that this rule is consistent with the regulatory philosophy and principles identified in Executive Order 12866 and in these two statutes. As shown in the following paragraphs, the rule will not be significant as defined by the Executive order and the Unfunded Mandates Reform Act, and the agency certifies that the rule will not have a significant economic impact on a substantial number of small entities.

The purpose of the rule is to implement section 506A of the act and to reduce the number of manufacturing changes subject to supplements requiring FDA approval prior to product distribution. The rule affects all drug manufacturers that submit manufacturing supplements and will result in a substantial reduction in burdens to applicants making manufacturing changes subject to the regulation. The rule permits earlier implementation of the changes and quicker marketing of products improved by manufacturing or labeling modifications. Faster implementation can result in marked gains in production efficiency. For example, a report by the Eastern Research Group, Inc. (ERG), an FDA contractor, on the effects of the SUPAC–IR found that reducing the number of changes that require preapproval gives companies greater control over their production resources, which could lead to significant net savings to industry (ERG, *Pharmaceutical Industry Cost Savings Through Use of the Scale-Up and Post-Approval Guidance for Immediate Release Solid Oral Dosage Forms (SUPAC–IR)*, January 7, 1998, Contract No. 223–94–8301). ERG estimated that companies may already have saved $71 million in 1997 due to the agency's implementation of more flexible reporting procedures for chemistry, manufacturing, and control changes. This rule would lead to additional savings because it expands these changes to other drug products to improve product labeling and manufacturing methods.

Because the rule will benefit manufacturers regardless of size and impose no additional costs, the agency certifies that this rule will not have a significant adverse economic impact on a substantial number of small entities.

VI. Paperwork Reduction Act of 1995

This final rule contains collections of information that are subject to review by OMB under the PRA (44 U.S.C. 3501–3520). "Collection of information" includes any request or requirement that persons obtain, maintain, retain, or report information to the agency, or disclose information to a third party or to the public (44 U.S.C. 3502(3) and 5 CFR 1320.3(c)). The title, description, and respondent description of the information collection are shown under this section of the document with an estimate of the annual reporting burden. Included in the estimate is the time for reviewing instructions, gathering and maintaining the data needed, and completing and reviewing the collection of information.

Title: Supplements and Other Changes to an Approved Application.

Description: The final rule sets forth requirements for manufacturing changes requiring supplement submission and FDA approval prior to the distribution of the product made using the change, changes requiring supplement submission at least 30 days prior to the distribution of the product, changes requiring supplement submission at the time of distribution, and changes to be described in an annual report. The regulation reduces the rate of increase in the number of manufacturing changes subject to supplements and the overall number of supplements requiring FDA approval prior to product distribution. Many changes that are currently reported in supplements will be able to be reported in annual reports. Supplement submissions contain more burdensome reporting requirements than a submission through an annual report. The regulation will not increase the number of annual reports but will allow applicants to include in an annual report information currently required to be reported to the agency in a supplemental application. The number of manufacturing changes currently reported in supplements that will be reported in annual reports is approximately 1,283.

Sections 314.70(a)(2) and 601.12(a)(2) require, generally, that the holder of an approved application must assess the effects of a manufacturing change before distributing a drug product made with the change. This section implements section 506A(a)(1) and 506A(b) of the act, which require the holder of an approved application to validate the effects of a manufacturing change on the identity, strength, quality, purity, or potency of the drug as these factors may relate to the safety or effectiveness of the drug before distributing a drug made with the change. Under section 506A(d)(3)(A) of the act, information developed by the applicant to validate the effects of the change regarding identity, strength, quality, purity, and potency is required to be submitted to FDA as part of the supplement or annual report. Thus, estimates for validation requirements are included in the estimates for supplements and annual reports; no separate estimates are provided for §§ 314.70(a)(2) and 601.12(a)(2) in table 1 of this document. Furthermore, no estimates are required for the guidance entitled "Changes to an Approved NDA or ANDA," because it does not provide recommendations on the specific information that should be developed by the applicant to validate the effect of the change on the identity, strength (e.g., assay, content uniformity), quality (e.g., physical, chemical, and biological properties), purity (e.g., impurities and degradation products), or potency (e.g., biological activity, bioavailability, bioequivalence) of a product as they may relate to the safety or effectiveness of the product.

Sections 314.70(a)(4) and 601.12(a)(4) require, generally, that the applicant must promptly revise all promotional labeling and advertising to make it consistent with any labeling changes implemented. The transmittal to FDA of advertisements and promotional labeling for drugs and biologics is accompanied by Form FDA 2253 and regulated by §§ 314.81(b)(3)(i) and 601.12(f)(4). This information collection

is approved by OMB until October 31, 2004, under OMB control number 0910–0376. Therefore, the burden for this requirement is not estimated in table 1 of this document.

Section 314.70(a)(5) requires the applicant to include in each supplement (except for a supplement providing for a change in the labeling) and amendment to each supplement a statement certifying that a field copy has been provided in accordance with § 314.440(a)(4). The information collection for submitting a field copy under § 314.440(a)(4) is approved by OMB until March 31, 2005, under OMB control number 0910–0001. Based on data concerning the number of supplements and amendments to supplements currently received by the agency, FDA estimates that approximately 8,556 certifications will be submitted annually as required by § 314.70(a)(5). FDA estimates that approximately 594 applicants will submit these certifications. FDA estimates that preparation of a statement certifying the field copy will take applicants an average of 5 minutes.

Sections 314.70(a)(6) and 601.12(a)(5) require the applicant to include a list of all changes contained in the supplement or annual report; for supplements, this list must be provided in the cover letter. The information collection for submitting an annual report under § 314.81(b)(2) is approved by OMB until March 31, 2005, under OMB control number 0910–0001. Based on data concerning the number of supplements currently received by the agency, FDA estimates that approximately 4,984 lists of all changes in the supplement will be submitted annually as required by § 314.70(a)(6). FDA estimates that approximately 594 applicants will submit these lists. Because the information required would be generated in preparing the supplement, the agency estimates that, under § 314.70(a)(6), it will take approximately 1 hour to include a list of changes in a cover letter for a supplement. FDA estimates that approximately 2,983 lists of all changes in the supplement or annual report will be submitted annually as required by § 601.12(a)(5). FDA estimates that approximately 190 applicants will submit these lists. Because the information required would be generated in preparing the supplement or annual report, the agency estimates that, under § 601.12(a)(5), it will take approximately 1 hour to include a list of changes for a supplement or an annual report.

Section 314.70(b) and current § 601.12(b) set forth requirements for changes requiring supplement submission and approval prior to distribution of the product made using the change (major changes). Section 314.70(b)(1) and current § 601.12(b)(1) provide, generally, that a supplement must be submitted for any change in the drug substance, drug product, production process, quality controls, equipment, or facilities that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. Section 314.70(b)(3) and current § 601.12(b)(3) specify the information that must be contained in the supplement.

Based on data concerning the number of supplements currently received by the agency, FDA estimates that approximately 1,744 supplements will be submitted annually under § 314.70(b)(1) and (b)(3). FDA estimates that approximately 594 applicants will submit such supplements, and that it will take approximately 150 hours to prepare and submit to FDA each supplement. FDA estimates that approximately 903 supplements will be submitted annually under § 601.12(b)(1) and (b)(3). FDA estimates that approximately 190 applicants will submit such supplements, and that it will take approximately 150 hours to prepare and submit to FDA each supplement.

Under §§ 314.70(b)(4) and 601.12(b)(4), an applicant may ask FDA to expedite its review of a supplement for public health reasons or if a delay in making the change described in it would impose an extraordinary hardship on the applicant. Such a supplement and its mailing cover should be marked: "Prior Approval Supplement-Expedited Review Requested." The burden for an applicant's request for an expedited review of a supplement by marking the mailing cover is minimal and is included in the burden hour estimates for submitting a supplement under § 314.70(b)(1) and (b)(3) and § 601.12(b)(1) and (b)(3).

Section 314.70(c) and current § 601.12(c) set forth requirements for changes requiring supplement submission at least 30 days prior to distribution of the product made using the change (moderate changes). Section 314.70(c)(1) and current § 601.12(c)(1) require, generally, that a supplement must be submitted for any change in the drug substance, drug product, production process, quality controls, equipment, or facilities that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. Under § 314.70(c)(3) and current § 601.12(c)(1), the supplement must give a full explanation of the basis for the change and identify the date on which the change is to be made. The supplement must be labeled "Supplement—Changes Being Effected in 30 Days." Under § 314.70(c)(4) and current § 601.12(c)(3), the information listed previously for § 314.70(b)(3) and current § 601.12(b)(3) must be contained in the supplement.

Based on data concerning the number of supplements currently received by the agency, FDA estimates that approximately 2,754 supplements will be submitted annually under § 314.70(c)(1), (c)(3), and (c)(4). FDA estimates that approximately 594 applicants will submit such supplements, and that it will take approximately 95 hours to prepare and submit to FDA each supplement. FDA estimates that approximately 255 supplements will be submitted annually under § 601.12(c)(1) and (c)(3). FDA estimates that approximately 98 applicants will submit such supplements, and that it will take approximately 95 hours to prepare and submit to FDA each supplement.

Under § 314.70(c)(6) and current § 601.12(c)(5), FDA may designate a category of changes for the purpose of providing that, in the case of a change in such category, the holder of an approved application may commence distribution of the drug product upon receipt by the agency of a supplement for the change. The supplement must be labeled "Supplement—Changes Being Effected." If the supplement provides for a labeling change, 12 copies of the final printed labeling must be included.

Based on data concerning the number of supplements currently received by the agency, FDA estimates that approximately 486 supplements will be submitted annually under § 314.70(c)(6). FDA estimates that approximately 486 applicants will submit such supplements, and that it will take approximately 95 hours to prepare and submit to FDA each supplement. FDA estimates that approximately 47 supplements will be submitted annually under § 601.12(c)(5). FDA estimates that approximately 34 applicants will submit such supplements, and that it will take approximately 95 hours to prepare and submit to FDA each supplement.

Section 314.70(d) and current § 601.12(d) set forth requirements for changes to be described in an annual report (minor changes). Section 314.70(d)(1) and current § 601.12(d)(1)

provide, generally, that changes in the drug substance, drug product, production process, quality controls, equipment, or facilities that have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product must be documented in the next annual report. Section 314.70(d)(3) and current § 601.12(d)(3) (including proposed § 601.12(d)(3)(iii)) list the information that must be included in the annual report for describing changes under this section.

Based on data concerning the number of supplements and annual reports currently received by the agency, FDA estimates that approximately 6,929 annual reports will include documentation of certain manufacturing changes as required under § 314.70(d)(1) and (d)(3). FDA estimates that approximately 704 applicants will submit such information, and that it will take approximately 35 hours to prepare and submit to FDA the information for each annual report. FDA estimates that approximately 227 annual reports will include documentation of certain manufacturing changes as required under current § 601.12(d)(1) and (d)(3). FDA estimates that approximately 166 applicants will submit such information, and that it takes approximately 35 hours to prepare and submit to FDA the information for each annual report.

Section 314.70(e) and current § 601.12(e) state, generally, that an applicant may submit one or more protocols describing the specific tests and studies and acceptance criteria to be achieved to demonstrate the lack of adverse effect for specified types of manufacturing changes on the identity, strength, quality, purity, and potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. Any such protocols, if not included in the approved application, or changes to an approved protocol, must be submitted as a supplement requiring approval from FDA prior to distribution of a drug product produced with the manufacturing change. The supplement, if approved, may subsequently justify a reduced reporting category for the particular change because the use of the protocol for that type of change reduces the potential risk of an adverse effect.

Based on data concerning the number of supplements currently received by the agency, FDA estimates that approximately 50 protocols will be submitted annually under § 314.70(e). FDA estimates that approximately 50 applicants will submit such protocols, and that it will take approximately 200 hours to prepare and submit to FDA each protocol. FDA estimates that approximately 20 protocols will be submitted annually under § 601.12(e). FDA estimates that approximately 14 applicants will submit such protocols, and that it will take approximately 200 hours to prepare and submit to FDA each protocol.

Current § 601.12(f) sets forth the requirements for supplement submission for labeling changes for biological products. Current § 601.12(f)(2)(i)(A) through (f)(2)(i)(D) specify those labeling changes for which an applicant must submit a supplement to FDA at the time the change is made. Section 601.12(f)(2)(i)(E) adds to these types of changes "any labeling change normally requiring a supplement submission and approval prior to distribution of the product that FDA specifically requests be submitted under this provision." Based on data concerning the number of supplements currently received by the agency, FDA estimates that approximately 12 labeling supplements will be submitted annually under current § 601.12(f)(1). FDA estimates that approximately 12 applicants will submit these supplements, and that it will take approximately 40 hours to prepare and submit to FDA each supplement. FDA estimates that approximately 10 labeling supplements will be submitted annually under current § 601.12(f)(2), including those that will be submitted under new § 601.12(f)(2)(i)(E). FDA estimates that approximately 10 applicants will submit these supplements, and that it will take approximately 20 hours to prepare and submit to FDA each supplement. FDA estimates that approximately 100 annual reports for labeling changes will be submitted under current § 601.12(f)(3). FDA estimates that approximately 70 applicants will submit these reports, and that it will take approximately 10 hours to prepare and submit to FDA each report. FDA estimates that approximately 1,495 labeling supplements will be submitted annually under current § 601.12(f)(4). FDA estimates that approximately 61 applicants will submit these supplements, and that it will take approximately 10 hours to prepare and submit to FDA each supplement.

Section 314.70(f) states that an applicant must comply with the patent information requirements under section 505(c)(2) of the act. Section 314.70(g) states that an applicant must include any applicable exclusivity information with a supplement as required under § 314.50(j). Patent and exclusivity information collection requirements are approved by OMB until March 31, 2005, under OMB control number 0910–0001. Therefore, this requirement is not estimated in table 1 of this document.

Comments Received on FDA's Proposed Information Collection Burden Estimates:

Concerning the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used, one comment said that FDA has underestimated the information collection burden. The comment suggested the following revised estimates: For § 314.70(b)(1) and (b)(3), the comment estimated 160 hours per response; for § 314.70(c)(1), (c)(3), and (c)(4), 80 hours per response; for § 314.70(c)(6), 80 hours per response; for § 314.70(d)(1) and (d)(3), 25 hours per response; for § 314.70(e), 240 hours per response. The comment assumed that the number of hours estimated refers to the number of hours required by regulatory affairs personnel to collect, assemble, and prepare data required for a submission. Other related activities, such as manufacturing validation lots and conducting stability studies, are not part of the estimates, since they are manufacturing activities that would be conducted, as appropriate, regardless of the reporting requirements. The comment said its estimates are based on an average time required for submissions, and the actual time required for a particular submission can vary, based on the complexity of the submitted change. The comment said that although the proposal would change the reporting level of changes, the associated "paperwork" for these changes is not significantly reduced and in some cases is increased.

Concerning the proposed requirement in § 314.70(e) that an applicant may submit one or more protocols, the comment noted that these protocols must be submitted as a supplement requiring approval from FDA prior to distribution of a drug produced with the manufacturing change. The comment said that, based on its experience, the estimate of 20 hours for these protocol submissions is significantly underestimated and that 240 hours is a more reasonable estimate. The comment said that these protocols are, in effect, supplements requiring prior approval and, therefore, would require the same number of hours to prepare as a prior approval supplement under § 314.70(b)(1) and (b)(3). Additionally, once the data for the change has been generated, the change requires an additional submission in order to implement the change. Assuming the data generated could be submitted

under § 314.70(c), the number of hours to submit changes under proposed § 314.70(e) would be a combination of the number of hours required to submit a change under § 314.70(b) and (c).

Another comment said that the estimated time in the proposal to collect the requested information for each type of supplement is low. The comment said that FDA underestimated the time to prepare the documents addressed in the proposal and that FDA should take greater care in evaluating the necessary steps required in preparing a supplement or report, not just the document preparation. For prior approved supplements under § 314.70(b), the comment said that the estimate of 80 hours is low and should be increased by at least 10 hours. The only time saving that can be gained under this requirement is when a firm can submit multiple supplements for the same change (site change), which is an uncommon occurrence; smaller firms submit one supplement at a time. For changes-being-effected supplements under § 314.70(c), the comment said that 50 hours for these types of supplements is low. The comment asked what is the difference between this type of supplement and prior approval supplements other than the filing mechanism. For annual reports under § 314.70(d), the comment said that 10 hours is low and that the data that go into such a report is collected over the entire year before the report may be put together. The comment said that an average of 20 hours is more reasonable. Concerning protocols under § 314.70(e), the comment said that 20 hours to prepare a suitability protocol is a large underestimate, and that firms will spend a large amount of time to determine just which tests and specifications to include in the protocol, in addition to preparing the protocol itself. The comment also said that the analysis and reporting of the results of the completed protocols was not included in the estimate.

FDA has considered the above comments as well as other information it has received and has revised the proposed information collection burden estimates. The estimate for "hours per response" for §§ 314.70(b)(1) and (b)(3) and 601.12(b)(1) and (b)(3) has been increased from 80 hours to 150 hours; the estimate for §§ 314.70(c)(1), (c)(3), and (c)(4) and 601.12(c)(1) and (c)(3) has been increased from 50 hours to 95 hours; the estimate for §§ 314.70(c)(6) and 601.12(c)(5) has been increased from 50 hours to 95 hours; the estimate for §§ 314.70(d)(1) and (d)(3) and 601.12(d)(1) and (d)(3) has been increased from 10 hours to 35 hours; and the estimate for §§ 314.70(e) and 601.12(e) has been increased from 20 hours to 200 hours.

Description of Respondents: Business or other for-profit organizations.

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN[1]

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Hours per Response	Total Hours
314.70(a)(5)	594	14	8,556	5 minutes	713
314.70(a)(6)	594	8	4,984	1	4,984
314.70(b)(1), (b)(3)	594	3	1,744	150	261,600
314.70(c)(1), (c)(3), (c)(4)	594	5	2,754	95	261,630
314.70(c)(6)	486	1	486	95	46,170
314.70(d)(1), (d)(3)	704	10	6,929	35	242,515
314.70(e)	50	1	50	200	10,000
601.12(a)(5)	190	16	2,983	1	2,983
601.12(b)(1), (b)(3)	190	5	903	150	135,450
601.12(c)(1), (c)(3)	98	3	255	95	24,225
601.12(c)(5)	34	1	47	95	4,465
601.12(d)(1), (d)(3)	166	1	227	35	7,945
601.12(e)	14	1	20	200	4,000
601.12(f)(1)	12	1	12	40	480
601.12(f)(2)	10	1	10	20	200
601.12(f)(3)	70	1	100	10	1,000
601.12(f)(4)	61	25	1,495	10	14,950
Total					1,023,310

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

The information collection provisions in this final rule have been approved under OMB control number 0910–0538. This approval expires August 31, 2005. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

VII. Environmental Impact

The agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VIII. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency has concluded that the rule does not contain policies that have federalism implications as defined in the order, and, consequently, a federalism summary impact statement is not required.

List of Subjects

21 CFR Parts 206 and 250

Drugs.

21 CFR Part 314

Administrative practice and procedure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

21 CFR Part 600

Biologics, Reporting and recordkeeping requirements.

21 CFR Part 601

Administrative practice and procedure, Biologics, Confidential business information.

■ Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 206, 250, 314, 600, and 601 are amended as follows:

PART 206—IMPRINTING OF SOLID ORAL DOSAGE FORM DRUG PRODUCTS FOR HUMAN USE

■ 1-3. The authority citation for 21 CFR part 206 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 355, 371; 42 U.S.C. 262.

§ 206.10 [Amended]

■ 4. Section 206.10 *Code imprint required* is amended in the first sentence of paragraph (b) by removing the phrase "§ 314.70(b)(2)(xi) or (b)(2)(xii)" and by adding in its place the phrase "§ 314.70(b)".

PART 250—SPECIAL REQUIREMENTS FOR SPECIFIC HUMAN DRUGS

■ 5. The authority citation for 21 CFR part 250 continues to read as follows:

Authority: 21 U.S.C. 321, 336, 342, 352, 353, 355, 361(a), 362(a) and (c), 371, 375(b).

§ 250.250 [Amended]

■ 6. Section 250.250 *Hexachlorophene, as a component of drug and cosmetic products* is amended in the last sentence of paragraph (c)(4)(ii) by removing the phrase "§ 314.70(c)(2)" and by adding in its place the phrase "§ 314.70(c)(6)(iii)".

PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG

■ 7. The authority citation for 21 CFR part 314 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 355a, 356, 356a, 356b, 356c, 371, 374, 379e.

■ 8. Section 314.3 is amended in paragraph (b) by alphabetically adding the definitions for "Assess the effects of the change" and "Specification" to read as follows:

§ 314.3 Definitions.

* * * * *

(b) * * *

Assess the effects of the change means to evaluate the effects of a manufacturing change on the identity, strength, quality, purity, and potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

* * * * *

Specification means the quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, components, in-process materials, container closure systems, and other materials used in the production of a drug substance or drug product. For the purpose of this definition, *acceptance criteria*means numerical limits, ranges, or other criteria for the tests described.

* * * * *

■ 9. Section 314.50 is amended:

■ a. In paragraph (d)(1)(ii)(*b*) by removing the phrase "specifications and test procedures" and by adding in its place the word "specification";

■ b. In paragraph (d)(1)(v) by removing the phrase "Except for a foreign applicant, the" and by adding in its place the word "The";

■ c. In paragraph (d)(3)(i) by adding the word "procedures" after the word "analytical";

■ d. In paragraph (d)(3)(ii) by removing the phrases "specifications or analytical methods" and "specification or analytical methods" each time they appear and by adding in their places the phrase "tests, analytical procedures, and acceptance criteria";

■ e. In paragraph (d)(4)(iv) by removing the word "methods" and by adding in its place the word "procedures";

■ f. In the last sentence of paragraph (e)(1) introductory text and in the first sentence of paragraph (e)(2)(i) by removing the word "methods" each time it appears and by adding in its place the word "procedures"; and

■ g. By revising the first two sentences of paragraphs (d)(1)(i) and (d)(1)(ii)(*a*) to read as follows:

§ 314.50 Content and format of an application.

* * * * *

(d) * * *

(1) * * *

(i) *Drug substance.* A full description of the drug substance including its physical and chemical characteristics and stability; the name and address of its manufacturer; the method of synthesis (or isolation) and purification of the drug substance; the process controls used during manufacture and packaging; and the specifications necessary to ensure the identity, strength, quality, and purity of the drug substance and the bioavailability of the drug products made from the substance, including, for example, tests, analytical procedures, and acceptance criteria relating to stability, sterility, particle size, and crystalline form. The application may provide additionally for the use of alternatives to meet any of these requirements, including alternative sources, process controls, and analytical procedures.* * *

(ii)(a) *Drug product.* A list of all components used in the manufacture of the drug product (regardless of whether they appear in the drug product) and a statement of the composition of the drug product; the specifications for each component; the name and address of each manufacturer of the drug product; a description of the manufacturing and packaging procedures and in-process controls for the drug product; the specifications necessary to ensure the identity, strength, quality, purity, potency, and bioavailability of the drug product, including, for example, tests, analytical procedures, and acceptance criteria relating to sterility, dissolution rate, container closure systems; and stability data with proposed expiration

dating. The application may provide additionally for the use of alternatives to meet any of these requirements, including alternative components, manufacturing and packaging procedures, in-process controls, and analytical procedures. * * *

* * * * *

§ 314.60 [Amended]

■ 10. Section 314.60 *Amendments to an unapproved application* is amended in paragraph (c) by removing the phrase ", other than a foreign applicant,".

■ 11. Section 314.70 is revised to read as follows:

§ 314.70 Supplements and other changes to an approved application.

(a) *Changes to an approved application.* (1) The applicant notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application. The notice is required to describe the change fully. Depending on the type of change, the applicant must notify FDA about it in a supplement under paragraph (b) or (c) of this section or by inclusion of the information in the annual report to the application under paragraph (d) of this section.

(2) The holder of an approved application under section 505 of the act must assess the effects of the change before distributing a drug product made with a manufacturing change.

(3) Notwithstanding the requirements of paragraphs (b) and (c) of this section, an applicant must make a change provided for in those paragraphs in accordance with a regulation or guidance that provides for a less burdensome notification of the change (for example, by submission of a supplement that does not require approval prior to distribution of the product or in an annual report).

(4) The applicant must promptly revise all promotional labeling and advertising to make it consistent with any labeling change implemented in accordance with paragraphs (b) and (c) of this section.

(5) Except for a supplement providing for a change in the labeling, the applicant must include in each supplement and amendment to a supplement providing for a change under paragraph (b) or (c) of this section a statement certifying that a field copy has been provided in accordance with § 314.440(a)(4).

(6) A supplement or annual report must include a list of all changes contained in the supplement or annual report. For supplements, this list must be provided in the cover letter.

(b) *Changes requiring supplement submission and approval prior to distribution of the product made using the change (major changes).* (1) A supplement must be submitted for any change in the drug substance, drug product, production process, quality controls, equipment, or facilities that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product.

(2) These changes include, but are not limited to:

(i) Except those described in paragraphs (c) and (d) of this section, changes in the qualitative or quantitative formulation of the drug product, including inactive ingredients, or in the specifications provided in the approved application;

(ii) Changes requiring completion of studies in accordance with part 320 of this chapter to demonstrate the equivalence of the drug product to the drug product as manufactured without the change or to the reference listed drug;

(iii) Changes that may affect drug substance or drug product sterility assurance, such as changes in drug substance, drug product, or component sterilization method(s) or an addition, deletion, or substitution of steps in an aseptic processing operation;

(iv) Changes in the synthesis or manufacture of the drug substance that may affect the impurity profile and/or the physical, chemical, or biological properties of the drug substance;

(v) The following labeling changes:

(A) Changes in labeling, except those described in paragraphs (c)(6)(iii), (d)(2)(ix), or (d)(2)(x) of this section;

(B) If applicable, any change to a Medication Guide required under part 208 of this chapter, except for changes in the information specified in § 208.20(b)(8)(iii) and (b)(8)(iv) of this chapter.

(vi) Changes in a drug product container closure system that controls the drug product delivered to a patient or changes in the type (e.g., glass to high density polyethylene (HDPE), HDPE to polyvinyl chloride, vial to syringe) or composition (e.g., one HDPE resin to another HDPE resin) of a packaging component that may affect the impurity profile of the drug product.

(vii) Changes solely affecting a natural product, a recombinant DNA-derived protein/polypeptide, or a complex or conjugate of a drug substance with a monoclonal antibody for the following:

(A) Changes in the virus or adventitious agent removal or inactivation method(s);

(B) Changes in the source material or cell line; and

(C) Establishment of a new master cell bank or seed.

(viii) Changes to a drug product under an application that is subject to a validity assessment because of significant questions regarding the integrity of the data supporting that application.

(3) The applicant must obtain approval of a supplement from FDA prior to distribution of a drug product made using a change under paragraph (b) of this section. Except for submissions under paragraph (e) of this section, the following information must be contained in the supplement:

(i) A detailed description of the proposed change;

(ii) The drug product(s) involved;

(iii) The manufacturing site(s) or area(s) affected;

(iv) A description of the methods used and studies performed to assess the effects of the change;

(v) The data derived from such studies;

(vi) For a natural product, a recombinant DNA-derived protein/polypeptide, or a complex or conjugate of a drug substance with a monoclonal antibody, relevant validation protocols and a list of relevant standard operating procedures must be provided in addition to the requirements in paragraphs (b)(3)(iv) and (b)(3)(v) of this section; and

(vii) For sterilization process and test methodologies related to sterilization process validation, relevant validation protocols and a list of relevant standard operating procedures must be provided in addition to the requirements in paragraphs (b)(3)(iv) and (b)(3)(v) of this section.

(4) An applicant may ask FDA to expedite its review of a supplement for public health reasons or if a delay in making the change described in it would impose an extraordinary hardship on the applicant. Such a supplement and its mailing cover should be plainly marked: "Prior Approval Supplement-Expedited Review Requested."

(c) *Changes requiring supplement submission at least 30 days prior to distribution of the drug product made using the change (moderate changes).* (1) A supplement must be submitted for any change in the drug substance, drug product, production process, quality controls, equipment, or facilities that has a moderate potential to have an adverse effect on the identity, strength,

quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. If the supplement provides for a labeling change under paragraph (c)(6)(iii) of this section, 12 copies of the final printed labeling must be included.

(2) These changes include, but are not limited to:

(i) A change in the container closure system that does not affect the quality of the drug product, except those described in paragraphs (b) and (d) of this section; and

(ii) Changes solely affecting a natural protein, a recombinant DNA-derived protein/polypeptide or a complex or conjugate of a drug substance with a monoclonal antibody, including:

(A) An increase or decrease in production scale during finishing steps that involves different equipment; and

(B) Replacement of equipment with that of a different design that does not affect the process methodology or process operating parameters.

(iii) Relaxation of an acceptance criterion or deletion of a test to comply with an official compendium that is consistent with FDA statutory and regulatory requirements.

(3) A supplement submitted under paragraph (c)(1) of this section is required to give a full explanation of the basis for the change and identify the date on which the change is to be made. The supplement must be labeled "Supplement—Changes Being Effected in 30 Days" or, if applicable under paragraph (c)(6) of this section, "Supplement—Changes Being Effected."

(4) Pending approval of the supplement by FDA, except as provided in paragraph (c)(6) of this section, distribution of the drug product made using the change may begin not less than 30 days after receipt of the supplement by FDA. The information listed in paragraphs (b)(3)(i) through (b)(3)(vii) of this section must be contained in the supplement.

(5) The applicant must not distribute the drug product made using the change if within 30 days following FDA's receipt of the supplement, FDA informs the applicant that either:

(i) The change requires approval prior to distribution of the drug product in accordance with paragraph (b) of this section; or

(ii) Any of the information required under paragraph (c)(4) of this section is missing; the applicant must not distribute the drug product made using the change until the supplement has been amended to provide the missing information.

(6) The agency may designate a category of changes for the purpose of providing that, in the case of a change in such category, the holder of an approved application may commence distribution of the drug product involved upon receipt by the agency of a supplement for the change. These changes include, but are not limited to:

(i) Addition to a specification or changes in the methods or controls to provide increased assurance that the drug substance or drug product will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess;

(ii) A change in the size and/or shape of a container for a nonsterile drug product, except for solid dosage forms, without a change in the labeled amount of drug product or from one container closure system to another;

(iii) Changes in the labeling to accomplish any of the following:

(A) To add or strengthen a contraindication, warning, precaution, or adverse reaction;

(B) To add or strengthen a statement about drug abuse, dependence, psychological effect, or overdosage;

(C) To add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product;

(D) To delete false, misleading, or unsupported indications for use or claims for effectiveness; or

(E) Any labeling change normally requiring a supplement submission and approval prior to distribution of the drug product that FDA specifically requests be submitted under this provision.

(7) If the agency disapproves the supplemental application, it may order the manufacturer to cease distribution of the drug product(s) made with the manufacturing change.

(d) *Changes to be described in an annual report (minor changes).* (1) Changes in the drug substance, drug product, production process, quality controls, equipment, or facilities that have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product must be documented by the applicant in the next annual report in accordance with § 314.81(b)(2).

(2) These changes include, but are not limited to:

(i) Any change made to comply with a change to an official compendium, except a change described in paragraph (c)(2)(iii) of this section, that is consistent with FDA statutory and regulatory requirements.

(ii) The deletion or reduction of an ingredient intended to affect only the color of the drug product;

(iii) Replacement of equipment with that of the same design and operating principles except those equipment changes described in paragraph (c) of this section;

(iv) A change in the size and/or shape of a container containing the same number of dosage units for a nonsterile solid dosage form drug product, without a change from one container closure system to another;

(v) A change within the container closure system for a nonsterile drug product, based upon a showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium;

(vi) An extension of an expiration dating period based upon full shelf life data on production batches obtained from a protocol approved in the application;

(vii) The addition or revision of an alternative analytical procedure that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application, or deletion of an alternative analytical procedure;

(viii) The addition by embossing, debossing, or engraving of a code imprint to a solid oral dosage form drug product other than a modified release dosage form, or a minor change in an existing code imprint;

(ix) A change in the labeling concerning the description of the drug product or in the information about how the drug product is supplied, that does not involve a change in the dosage strength or dosage form; and

(x) An editorial or similar minor change in labeling.

(3) For changes under this category, the applicant is required to submit in the annual report:

(i) A statement by the holder of the approved application that the effects of the change have been assessed;

(ii) A full description of the manufacturing and controls changes, including the manufacturing site(s) or area(s) involved;

(iii) The date each change was implemented;

(iv) Data from studies and tests performed to assess the effects of the change; and,

(v) For a natural product, recombinant DNA-derived protein/polypeptide, complex or conjugate of a drug substance with a monoclonal antibody, sterilization process or test methodology

related to sterilization process validation, a cross-reference to relevant validation protocols and/or standard operating procedures.

(e) *Protocols.* An applicant may submit one or more protocols describing the specific tests and studies and acceptance criteria to be achieved to demonstrate the lack of adverse effect for specified types of manufacturing changes on the identity, strength, quality, purity, and potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. Any such protocols, if not included in the approved application, or changes to an approved protocol, must be submitted as a supplement requiring approval from FDA prior to distribution of a drug product produced with the manufacturing change. The supplement, if approved, may subsequently justify a reduced reporting category for the particular change because the use of the protocol for that type of change reduces the potential risk of an adverse effect.

(f) *Patent information.* The applicant must comply with the patent information requirements under section 505(c)(2) of the act.

(g) *Claimed exclusivity.* If an applicant claims exclusivity under § 314.108 upon approval of a supplement for change to its previously approved drug product, the applicant must include with its supplement the information required under § 314.50(j).

§ 314.81 [Amended]

■ 12. Section 314.81 *Other postmarketing reports* is amended in paragraph (b)(1)(ii) by removing the word "specifications" and by adding in its place the word "specification".

§ 314.94 [Amended]

■ 13. Section 314.94 *Content and format of an abbreviated application* is amended in the second sentence of paragraph (d)(2) by removing the word "methods" each time it appears and by adding in its place the word "procedures".

§ 314.410 [Amended]

■ 14. Section 314.410 *Imports and exports of new drugs* is amended in paragraph (b)(2) by removing the word "specifications" and by adding in its place the word "specification".

§ 314.430 [Amended]

■ 15. Section 314.430 *Availability for public disclosure of data and information in an application or abbreviated application* is amended in paragraph (e)(6) by removing the word "method" both times it appears and by adding in its place the word "procedure".

PART 600—BIOLOGICAL PRODUCTS: GENERAL

■ 16. The authority citation for 21 CFR part 600 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 360i, 371, 374; 42 U.S.C. 216, 262, 263, 263a, 264, 300aa–25.

■ 17. Section 600.3 is amended by adding paragraphs (jj) and (kk) to read as follows:

§ 600.3 Definitions.

* * * * *

(jj) *Assess the effects of the change*, as used in § 601.12 of this chapter, means to evaluate the effects of a manufacturing change on the identity, strength, quality, purity, and potency of a product as these factors may relate to the safety or effectiveness of the product.

(kk) *Specification*, as used in § 601.12 of this chapter, means the quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of products, intermediates, raw materials, reagents, components, in-process materials, container closure systems, and other materials used in the production of a product. For the purpose of this definition, *acceptance criteria* means numerical limits, ranges, or other criteria for the tests described.

PART 601—LICENSING

■ 18. The authority citation for 21 CFR part 601 continues to read as follows:

Authority: 15 U.S.C. 1451–1561; 21 U.S.C. 321, 351, 352, 353, 355, 356b, 360, 360c–360f, 360h–360j, 371, 374, 379e, 381; 42 U.S.C. 216, 241, 262, 263, 264; sec 122, Pub. L. 105–115, 111 Stat. 2322 (21 U.S.C. 355 note).

■ 19. Section 601.12 is amended by revising paragraphs (a), (b)(2)(i), (c)(2)(ii), (d)(2)(i) through (d)(2)(v), and (d)(2)(vii); by adding paragraphs (b)(4), (c)(2)(iv), (c)(6), (d)(3)(iii), and (f)(2)(i)(E); and by removing and reserving paragraph (c)(2)(i) to read as follows:

§ 601.12 Changes to an approved application.

(a) *General.* (1) As provided by this section, an applicant must inform the Food and Drug Administration (FDA) about each change in the product, production process, quality controls, equipment, facilities, responsible personnel, or labeling established in the approved license application(s).

(2) Before distributing a product made using a change, an applicant must assess the effects of the change and demonstrate through appropriate validation and/or other clinical and/or nonclinical laboratory studies the lack of adverse effect of the change on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product.

(3) Notwithstanding the requirements of paragraphs (b), (c), and (f) of this section, an applicant must make a change provided for in those paragraphs in accordance with a regulation or guidance that provides for a less burdensome notification of the change (for example, by submission of a supplement that does not require approval prior to distribution of the product or in an annual report).

(4) The applicant must promptly revise all promotional labeling and advertising to make it consistent with any labeling change implemented in accordance with paragraphs (f)(1) and (f)(2) of this section.

(5) A supplement or annual report must include a list of all changes contained in the supplement or annual report. For supplements, this list must be provided in the cover letter.

(b) * * *

(2) * * *

(i) Except as provided in paragraphs (c) and (d) of this section, changes in the qualitative or quantitative formulation, including inactive ingredients, or in the specifications provided in the approved application;

* * * * *

(4) An applicant may ask FDA to expedite its review of a supplement for public health reasons or if a delay in making the change described in it would impose an extraordinary hardship on the applicant. Such a supplement and its mailing cover should be plainly marked: "Prior Approval Supplement-Expedited Review Requested.

(c) * * *

(2) * * *

(i) [Reserved]

(ii) An increase or decrease in production scale during finishing steps that involves different equipment; and

* * * * *

(iv) Relaxation of an acceptance criterion or deletion of a test to comply with an official compendium that is consistent with FDA statutory and regulatory requirements.

* * * * *

(6) If the agency disapproves the supplemental application, it may order the manufacturer to cease distribution of

the products made with the manufacturing change.

(d) * * *

(2) * * *

(i) Any change made to comply with a change to an official compendium, except a change described in paragraph (c)(2)(iv) of this section, that is consistent with FDA statutory and regulatory requirements.

(ii) The deletion or reduction of an ingredient intended only to affect the color of the product, except that a change intended only to affect Blood Grouping Reagents requires supplement submission and approval prior to distribution of the product made using the change in accordance with the requirements set forth in paragraph (b) of this section;

(iii) An extension of an expiration dating period based upon full shelf life data on production batches obtained from a protocol approved in the application;

(iv) A change within the container closure system for a nonsterile product, based upon a showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium;

(v) A change in the size and/or shape of a container containing the same number of dosage units for a nonsterile solid dosage form product, without a change from one container closure system to another;

* * * * *

(vii) The addition or revision of an alternative analytical procedure that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application, or deletion of an alternative analytical procedure.

(3) * * *

(iii) A statement by the holder of the approved application or license that the effects of the change have been assessed.

* * * * *

(f) * * *

(2) * * *

(i) * * *

(E) Any labeling change normally requiring a supplement submission and approval prior to distribution of the product that FDA specifically requests be submitted under this provision.

Dated: March 24, 2004.

Jeffrey Shuren,

Assistant Commissioner for Policy.

[FR Doc. 04–7532 Filed 4–7–04; 8:45 am]

BILLING CODE 4160–01–S