

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 (part 610 (21 CFR part 610, subpart G)), 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 (in part 610, subpart G) 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. ~~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

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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.

~~FDA invites comments on the following topics: (1) Whether the collection of information is necessary for proper performance of FDA’s functions, including whether the information will have practical utility; (2) the accuracy of FDA’s estimate of the burden of the collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.~~

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*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 15, 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 15, 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 15, 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.

~~The information collection provisions in this rule in compliance with section 3507(d) of the PRA (44 U.S.C. 3507(d)), the agency has submitted a copy of this rule to OMB for its review and approval of these information collections. Interested persons are requested to fax comments regarding this collection of information, including suggestions for conduct or sponsor, and a person is not~~

Final rule have been approved under OMB control number 0910-0538. This approval expires August 31, 2005. An agency may not

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required to respond to, a collection of information reducing this burden, to the Office of Information and Regulatory Affairs, OMB unless it displays a currently valid OMB Control number. (see ADDRESSES), Attn: Fumie Yokota, Desk Officer for FDA. ✓ OMB

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN<sup>1</sup>

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

<sup>1</sup> There are no capital costs or operating and maintenance costs associated with this collection of information.

## 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 Part 5*

Authority delegations (Government agencies), Imports, Organization and functions (Government agencies).

#### *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 5, 206, 250, 314, 600, and 601 are amended as follows:

### **PART 5—DELEGATIONS OF AUTHORITY AND ORGANIZATION**

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

**Authority:** 5 U.S.C. 504, 552, App. 2 605; 7 U.S.C. 138a, 2217; 15 U.S.C. 638, 1261–1282, 1451–1461, 3701–3711a; 21 U.S.C., 61–63, 141–149, 301–394, 467f, 679(b), 801–886, 1031–1309, 1401–1403; 35 U.S.C. 156; 42 U.S.C. 238, 241, 242, 242a, 242l, 242n, 242o, 243, 262, 263, 264, 265, 300u–300u–5, 300aa–1, 300ar–25–28, 300cc, 300ff, 1395y, 4332, 4831(a), 10007–10008, E.O. 11921, 41 FR 24294, 3 CFR, 1977 Comp., p. 124–131; E.O. 12591, 52 FR 13414, 3 CFR, 1988 Comp., p. 220–223.

### **§ 5.80 [Amended]**

■ 2. Section 5.80 *Approval of new drug applications and their supplements* is amended in the first sentence of paragraphs (d) and (f) by removing the phrase “§§ 314.70(b)(1), (b)(2)(ii) through (b)(2)(x), (c)(1), and (c)(3)” and by adding in its place the phrase “§ 314.70(b)(1), (b)(2)(i) excluding changes in qualitative or quantitative formulation, (b)(2)(iii), (b)(2)(iv), (b)(2)(vi), (b)(2)(vii), (c)(2)(i), (c)(2)(ii), (c)(6)(i), and (c)(6)(ii)”; and in the first sentence of paragraph (e) by removing the phrase “§ 314.70(b)(3) and (c)(2)(i) through (c)(2)(iv)” and by adding in its place the phrase “§ 314.70(b)(2)(v) and (c)(6)(iii)”.

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

■ 3. The authority citation for 21 CFR part 206 is revised 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 is revised 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”; in paragraph (d)(3)(i) by adding the word “procedures” after the word “analytical”;

■ c. 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”;

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

■ e. 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

■ f. 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 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 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 overdose;

(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 (note: change consistent with proposal and current § 601.12(d)(3)(ii)).

(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 is revised 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 is revised 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 paragraph (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.

