DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 314, 600, 601, 610, and 640

[Docket No. 95N–0329]

RIN 0910–AA57

Changes to an Approved Application

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the biologics regulations for reporting changes to an approved application in order to reduce unnecessary reporting burdens on applicants holding licenses approved by the Center for Biologics Evaluation and Research (CBER) under the Public Health Service Act (the PHS Act) to manufacture biological products. In addition, FDA is amending the corresponding drug regulations for submitting supplements and reporting changes to an application approved under the Federal Food, Drug, and Cosmetic Act (the act) for specified biotechnology products reviewed in the Center for Drug Evaluation and Research (CDER) to harmonize the drugs and biologics regulations. This final rule is part of FDA's continuing effort to achieve the objectives of the President's ''Reinventing Government'' initiatives.

DATES: Effective Date: The regulation is effective October 7, 1997.

Compliance Date: Submit initial annual reports required by §§ 314.70(g)(3) and 601.12(d) and (f)(3) within 60 days of the first anniversary date of the approval of the application of the product occurring on or after January 20, 1998.

FOR FURTHER INFORMATION CONTACT:

Steven F. Falter, Center for Biologics Evaluation and Research (HFM–630), Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448, 301–594–3074,

or

Yuan Yuan Chiu, Center for Drug Evaluation and Research (HFD–800), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–0260.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of January 29, 1996 (61 FR 2739), FDA proposed to amend the biologics regulations in § 601.12 (21 CFR 601.12) for reporting to FDA changes to an approved application in order to reduce unnecessary reporting burdens on applicants holding licenses approved by CBER under the PHS Act to manufacture biological products. Similarly, FDA also proposed to amend the corresponding regulations applicable to drugs in § 314.70 (21 CFR 314.70) for reporting changes to an approved application for certain biotechnology products (identified in the proposed rule as ''well-characterized biotechnology products'') to reduce unnecessary reporting burdens and to harmonize the regulations applicable to biotechnology products. FDA issued the proposed rule as part of its response to several mandates to reduce the burdens associated with government regulation. These mandates include, the President's memorandum of March 4, 1995, announcing the ''Regulatory Reinvention Initiative;'' the President's memorandum of April 21, 1995, ''Regulatory Reform—Waiver of Penalties and Reduction of Reports;'' the April 1995 publication, ''Reinventing Drug and Medical Device Regulations;'' and the November 1995, Presidential National Performance Review report, ''Reinventing the Regulation of Drugs Made From Biotechnology.'' Each included elements intended to reduce regulatory burdens while assuring the continued safety and effectiveness of regulated products.

This final rule is part of FDA's continuing effort to achieve the objectives of the President's ''Reinventing Government'' initiative to harmonize regulations administered by CDER and CBER in FDA, to reduce unnecessary burdens, and to improve the consistency in the processes for complying with FDA's regulations without diminishing public health protection.

II. Proposed Rule

In the proposed rule of January 29, 1996, FDA proposed that for reporting purposes changes to an approved application be divided into three categories. In § 601.12(b), FDA proposed for a change that has a substantial potential to have an adverse effect on the safety, purity, potency, or effectiveness of the product, that a supplement to the approved application be submitted and that the product manufactured after the change not be distributed until the supplement is approved. In § 601.12(c), FDA proposed for a change that has a moderate potential to have an adverse effect on the safety, purity, potency, or effectiveness of the product, that FDA be notified in writing of a change not less than 30 days before distribution of the product made using the change. Proposed § 601.12(c)(2) provided that if any specified information in the notification is missing or if the type of change requires submission of a supplement and approval by FDA before implementation, the product may not be distributed until compliance with the requirements is achieved. In proposed § 601.12(d), changes that have a minimal potential to have an adverse effect on the safety, purity, potency, or effectiveness of the product would be reported in an annual report, submitted each year within 60 days of the anniversary date of the approval of the application. The information that would be included in the annual report was specified in proposed § 601.12(d)(1). In § 601.12(e), FDA proposed regulations similar to those discussed above applicable to changes in labeling. For clarity, FDA proposed in 21 CFR 600.3 to add definitions for ''amendment'' and ''supplement'' as the terms apply to license applications for biological products.

For consistency, FDA also proposed to amend the corresponding regulations applicable to drugs in § 314.70 for submitting supplements and reporting changes to an application approved under the act for certain biotechnology products reviewed in CDER (identified in the proposed rule as ''well-characterized biotechnology products'').

In the same issue of the **Federal Register** of January 29, 1996, (61 FR 2748 and 2749), FDA made available and invited public comment on two draft guidance documents entitled, ''Changes to an Approved Application for Well-Characterized Therapeutic Recombinant DNA-Derived and Monoclonal Antibody Biotechnology Products'' and ''Changes to an Approved Application.'' The draft guidance documents were intended to assist applicants in determining how they should report changes to an approved application under the revised regulations. Elsewhere in this issue of the **Federal Register**, FDA is announcing the availability of final guidance documents, revised from those proposed as a result of public comment, which are intended to aid applicants in complying with the requirements of this final rule.

In the **Federal Register** of March 28, 1996 (61 FR 13793), FDA announced a public meeting, held on April 19, 1996, to discuss and gather information and views on the proposed rule and draft guidance documents. A transcript of the public meeting is on file in the public docket identified in the heading of this

document at Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857.

III. Highlights and Summary of Changes in the Final Rule

Under the proposed rule, an applicant would be required to report a change by one of three mechanisms, depending on the potential for the change to have an adverse effect on the safety, purity, potency, or effectiveness of the product. Similarly, the final rule will require reporting of changes under one of three mechanisms, depending on the potential for the change to have an adverse effect on the ''identity, strength, quality, purity, or potency of the product, as they may relate to the safety or effectiveness of the product'' (hereinafter referred to in the document as ''the safety or effectiveness of the product'').

The scope of applicability of the changes to § 314.70 is being revised to identify the specific products, i.e., recombinant deoxyribonucleic acid (DNA)-derived protein/polypeptide products and complexes or conjugates of drugs with monoclonal antibodies regulated under the act, to which new § 314.70(g) applies. Monoclonal antibodies for in vivo use complexed or conjugated with radiopharmaceuticals or toxins would be covered by § 601.12 of the final rule.

Some changes in each category are identified in the final rule. Several of these changes differ from those changes identified in the proposed rule. Some of these changes were previously discussed in the draft guidance documents as FDA's interpretation of the types of changes FDA believed would fall into each category. Based on comments received, they are now included in the final rule to provide added clarity as to the types of changes which have a substantial, moderate, or minimal potential to have an adverse effect on the safety or effectiveness of a product.

The final rule provides for the use of a protocol, sometimes called a ''comparability protocol,'' which would describe the specific tests and validation studies and acceptable limits to be achieved to demonstrate the lack of adverse effect for specified types of changes on the safety or effectiveness of the product. Upon approval of the protocol, FDA may determine that certain changes evaluated in accordance with the protocol may be reported by a less burdensome means; for example, a change generally requiring preapproval by FDA could be made and the product distributed 30 days after receipt by FDA of the supplement reporting the change. For a change normally requiring a 30-day wait, use of the approved protocol could justify distribution at the time of receipt of the supplement by FDA. An approved comparability protocol may also be used, in some cases, to reduce the reporting category from requiring a 30-day supplement submission to an annual report submission.

For those changes that have a moderate potential to have an adverse effect on the safety or effectiveness of the product, the final rule will require the submission of a supplement subject to FDA approval, and the product made using the change may be distributed not less than 30 days after receipt of the supplement by FDA; or, in some cases, the product made using the change may be distributed immediately upon receipt of the supplement by FDA.

Similar to the proposed rule, changes that have a minimal potential to have an adverse effect on the safety or effectiveness of the product will be reported in an annual report, submitted within 60 days of the first year of date of approval of the application. The final rule also allows an applicant holding a license under section 351 of the PHS Act to request FDA approval to submit an annual report on a date other than the first year so that annual reports for multiple products may be combined in a single annual report submission.

The requirements for reporting changes to the labeling for biological products are basically unchanged from the proposed rule. One clarification is the form to be used for submission of advertisements and promotional labeling for biological products. Form FDA–2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use), the form specified in § 314.81(b)(3) (21 CFR 314.81(b)(3)), is currently under revision by the agency. When final, it will be used for both drug and biological products for submission of advertisements and promotional labeling. The final rule now states that ''Form FDA–2567 (Transmittal of Labels and Circulars) or an equivalent form shall be used.'' In the future, FDA intends that a revised Form FDA–2253 will be used instead of Form FDA–2567. A future **Federal Register** notice will announce the availability of the revised Form FDA–2253.

The final rule includes a conforming amendment to § 610.9 (21 CFR 610.9) for biological products subject to licensing, so that changes to methods and processes equivalent to those specified in the regulations may be submitted in accordance with § 601.12 in the final rule. Similarly, FDA is revising § 640.120 (21 CFR 640.120) so that an exception or alternative to the regulations applicable to blood, blood components, or blood products may be submitted, for licensed products, in accordance with § 601.12.

Other minor changes to improve the clarity and consistency of the regulations are also included throughout the final rule.

IV. Responses to Comments

FDA provided 90 days for the submission of written comments on the proposed rule. FDA also invited the submission of written comments at the public meeting of April 19, 1996. To ensure that there was adequate time for the submission of written comments resulting from the public meeting, as announced in the notice of the public meeting, FDA extended the comment period an additional 8 days, providing 98 days for public comment.

The transcript of the public meeting, written comments to the proposed rule, and comments submitted at or after the public meeting are on file in the Dockets Management Branch (address above).

FDA received eleven letters of comment in response to the proposed rule, including one letter filed in response to one of the guidance documents but which includes comments pertaining to the proposed rule. Comments received and FDA's responses to the comments are discussed below.

1. Two comments on proposed § 314.70(g) recommended that the term ''well-characterized biotechnology product'' be broadened to include additional products, consistent with the definition proposed by the Pharmaceutical Research and Manufacturers of America.

FDA has determined that it is more appropriate to clearly specify products covered by the final rule than to use a general term such as ''well-characterized biotechnology products.'' As proposed, § 314.70(g) would have applied only to those ''well-characterized biotechnology products'' which are regulated as new drugs, rather than as biologics. FDA has determined that defining such products is difficult and no longer uses the term in this or other regulations (see the final rule, Elimination of Establishment License Application for Specified Biotechnology and Specified Synthetic Biological Products (61 FR 24227, May 14, 1996), concerning appropriate terminology for these products). To clarify the regulation, FDA is amending § 314.70(g) in the final rule to identify the specific products to which paragraph (g) applies; i.e., recombinant DNA-derived protein/

polypeptide products or complexes and conjugates of drugs with monoclonal antibodies (where the primary mode of action is due to the drug). For all other drug products, including synthetic peptides and antisense nucleotides, the applicant will continue to report changes as provided in § 314.70(a) through (f). For monoclonal antibodies complexed or conjugated with radiopharmaceuticals or toxins, changes to approved applications will be reported under § 601.12.

2. Three comments requested additional clarification of what constitutes a ''substantial,'' ''moderate,'' and ''minimal'' potential to have an adverse effect on the product. The comments stated that further definition of the risks that are of concern to FDA are necessary to understand the regulation and that such clarification was preferable to providing exhaustive lists of examples of changes in agency guidance.

The regulations in the final rule apply to many types of changes for a broad spectrum of products, including many biotechnology products, vaccines, blood and blood components, and other biological products. The regulations will apply to products that are currently experimental or in the conceptual stages of development, which may have special concerns that FDA cannot, at this time, anticipate. The regulations are written to accommodate the many types of changes for such a broad range of products.

In addition, there is a need to preserve flexibility in the regulations to ensure that the least burdensome means for reporting changes are made available. FDA believes that this flexibility will ensure the continued improvement of the products involved. For example, a change that may currently be considered to have a substantial potential to have an adverse effect on the safety or effectiveness of the product may, at a later date, based on new information or advances in technology, be determined to have a lesser potential to have an adverse effect on the safety or effectiveness of the product. Conversely, a change now considered, for example, to have a moderate potential to have an adverse effect on the safety or effectiveness of the product may, based on information not available at this time, be later determined by the agency to have a substantial potential to have an adverse effect on a product.

FDA agrees there is a need to clarify the regulations to help identify those changes which have a substantial, moderate, or minimal potential to have an adverse effect on the safety or effectiveness of the product. In this regard, FDA has included examples of specific changes in the final rule in order to further clarify the types of changes that fall into each category and to provide further predictability about the application of the rule.

Many factors should be considered in determining whether a change has a substantial, moderate, or minimal potential to have an adverse effect on the safety or effectiveness of the product. For example, the level of knowledge about the product and its active components may affect the ability to assess the effect of a change. The type of change being made will also contribute to the risk of the change having an adverse effect. Some manufacturing changes have a greater potential to cause unwanted or unexpected changes to the product which may be difficult to assess by merely testing to specifications. The type of product is also a factor to consider in determining the potential risk of an adverse effect on the product. Some products can be adversely affected by small changes which may cause larger effects even though the changes may seem to be low risk. For example, a change in passage number for a live virus vaccine could affect the safety of the vaccine and this type of change may be difficult to assess.

Therefore, defining ''substantial,'' ''moderate,'' and ''minimal'' in the regulations with such specificity that they exhaustively describe all of the many individual changes that may occur is not feasible. However, as FDA gains experience in the use of this rule, it will consider whether to propose additional revisions to further clarify how to determine the appropriate submission for a change to an approved application.

At this time, FDA is clarifying the final regulations in several ways while providing adequate flexibility. The revisions are as follows:

a. *Clarification of wording.* FDA is amending the final rule by specifying a change in quality controls as a type of change within the scope of reporting provisions of the final rule. Similarly, for purposes of clarity and consistency, FDA is including in § 601.12(a), (b)(1), (c)(1), and (d)(1) a change in responsible personnel as subject to the requirements of the final rule. ''Responsible personnel'' was inadvertently included in only some, but not all, of the appropriate parts of the proposed rule.

FDA is further amending the final rule to specify that the mechanism for reporting a change is based on the degree of potential of the change ''to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product.'' ''Identity, strength, quality, purity, and potency'' are all elements that are assessed in determining the safety or effectiveness of the product. In addition, FDA is adding the term ''major changes'' to the headings of §§ 314.70(g)(1) and 601.12(b), and ''minor changes'' to the headings of §§ 314.70(g)(3) and 601.12(d), in order to further clarify the types of changes which would fall into each category.

b. *Inclusion of examples of changes falling under each reporting category.* In proposed §§ 314.70(g)(1)(i)(A), (g)(1)(i)(B), and (g)(1)(i)(C) and 601.12(b)(1)(i), (b)(1)(ii), and (b)(1)(iii), FDA specifically identified changes that would be among those subject to supplement submission and approval prior to distribution of the product made using the change. FDA has reevaluated the proposed regulations and has determined that, for purposes of clarification, more types of changes should be specifically identified in the regulations as being subject to supplement submission and approval prior to distribution of the product made using the change. Accordingly, the final rule provides in §§ 314.70(g)(1)(ii)(A) through (g)(1)(ii)(F) and 601.12(b)(2)(i) through (b)(2)(vi) more types of changes that FDA has determined are subject to submission of a supplement and approval by FDA prior to distribution of the product made using the change.

Similarly, FDA is including examples of changes that have a moderate potential or a minimal potential to have an adverse effect on the safety or effectiveness of a product in §§ 314.70(g)(2)(ii) and 601.12(c)(2), and §§ 314.70(g)(3)(ii) and 601.12(d)(2), respectively. These lists are not intended to be all inclusive but are examples of the types of changes that fall into each category

3. One comment recommended that proposed § 314.70(g) not be added to part 314 (21 CFR part 314). Instead, the comment suggested that changes related to any well-characterized biotechnology product, whether regulated as a drug or as a biologic, should be reported in accordance with existing § 314.70(a) through (f).

FDA disagrees in part with the comment. FDA agrees that biotechnology products should be regulated consistently but believes the regulations in the final rule are necessary to ensure the continued safety and effectiveness of recombinant DNA-derived protein/polypeptide products and complexes or conjugates of drugs with monoclonal antibodies. Products

manufactured using biotechnology can present somewhat different scientific issues than products manufactured using more traditional techniques. In new §§ 314.70(g) and 601.12, the agency is promulgating requirements appropriate for this category of product, whether regulated as a drug or biologic.

4. One comment on proposed §§ 314.70(g)(3) and 601.12(d) recommended that the requirements be amended to be consistent with current § 314.70(d)(1) so that changes made by an applicant to comply with an official compendium would be among those for which only notification in an annual report would be necessary.

FDA agrees with the comment and is including this change in §§ 314.70(g)(3)(ii) and 601.12(d)(2) of the final rule as one that may be reported in the annual report.

5. One comment on proposed § 601.12 suggested that the term ''effectiveness'' should not be used in reference to blood and plasma establishments. The comment stated that the effectiveness of a blood component can be greatly affected by circumstances of its use, which is entirely out of the control of the manufacturer and that Source Plasma, being a source material for the manufacture of other products, has no ''effectiveness'' in and of itself.

FDA disagrees with the comment. There are many examples of types of changes in manufacturing a blood or blood component product which may have an adverse effect on the effectiveness of the product. For example, any change that may affect the viability of Red Blood Cells, such as a change in dating period, anticoagulant, or processing methods, may directly affect the effectiveness of the product and the impact of the change should be evaluated accordingly. The comment is correct that Source Plasma is only used in the manufacture of other products and the ''effectiveness'' of Source Plasma is not by itself a consideration. However, inclusion of the ''effectiveness'' in the regulations has no effect upon the burdens associated with the regulations for Source Plasma or other intermediate products where effectiveness of the product is not directly a factor. FDA believes it is unnecessary to clarify further the regulations in this respect.

6. One comment disagreed with the examples of changes given in proposed § 601.12(b)(1), which would require submission of a supplement and approval by FDA before distribution of the product made using the change. The comment stated that most of the examples of changes should be reported as notifications to FDA rather than requiring preapproval.

FDA disagrees with the comment. The types of changes identified in § 601.12(b)(1) of the proposed rule and those in the final rule are based on FDA's experience of reviewing supplements and are those for which FDA believes there is a substantial potential to have an adverse effect on the safety or effectiveness of the product. Listing examples of the types of changes with such potential provides useful information to applicants for assessing the appropriate category of reporting.

However, FDA also recognizes there may be instances when the agency may determine that a reduced reporting category for a specific manufacturing change is justified for a type of change that is ordinarily subject to submission of a supplement and approval by FDA prior to distribution of the product made using the change.

If the agency can be assured that when a manufacturing change is implemented appropriate procedures have been followed by the applicant to evaluate the effect of the change on the safety or effectiveness of the product, FDA believes that in certain cases the potential for an adverse effect may be lessened.

Generally, when considering a change in the manufacture of a product, the manufacturer will prepare a protocol, often called a ''comparability protocol,'' identifying and describing the tests to be performed in evaluating the change and its effect on the product, and defining the criteria against which the impact of the change will be evaluated. By providing an opportunity for FDA to review and approve the comparability protocol before it is used by the applicant to evaluate a change, FDA can have greater assurance that the change is being properly evaluated and, therefore, that there is less potential for the change to have an adverse effect on the safety or effectiveness of the product.

Accordingly, FDA is adding §§ 314.70(g)(4) and 601.12(e) in the final rule to provide that an applicant may submit to FDA as a supplement a protocol 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 safety or effectiveness of the product. Upon approval of the protocol, FDA may determine that the use of the approved protocol for the particular change justifies the use of a reduced reporting category for that change because the use of the protocol reduces the potential risk of adverse effect.

The guidance documents being made available with this final rule provide examples of how, consistent with FDA's current interpretation of the rule, a comparability protocol approved by FDA may be used to justify a reduction in the reporting category. For example, use of an approved protocol for a particular change may result in a determination by FDA that a change usually subject to supplement submission and approval by FDA prior to distribution of the product made using the change may be submitted as a change subject to supplement submission at least 30 days prior to distribution of the product made using the change. Similarly, FDA is including in §§ 314.70(g)(2)(v) and 601.12(c)(5) in the final rule that use of a previously approved protocol is one means by which FDA may determine that a product made using a specified change may be distributed immediately upon receipt of the supplement by FDA (see also, FDA's response to comment 10 of this document for additional discussion of the means for permitting the immediate distribution of a product made using a change).

However, use of a comparability protocol approved by FDA may not justify a reduction in the reporting category for every type of change. Some steps in manufacturing a biological product are so critical to the safety and effectiveness of the product that a change in that manufacturing step would always be subject to the submission of a supplement to FDA and approval by FDA prior to distribution of the product made using the change.

7. Two comments related to proposed § 601.12(c), which would provide for notification to FDA of certain changes not less than 30 days before distribution of the product made using the change. The comments recommended that § 601.12(c) be deleted and that there be only two tiers of changes: Those requiring submission of a supplement and preapproval by FDA, and those which may be reported in an annual report. One of the comments recommended that, when other safety issues have been addressed, changes which result in a product meeting currently approved release criteria should be reported in an annual report. One of the comments noted that, in effect, the submission of a notification was equivalent in reporting burden to the submission of a supplement.

FDA disagrees with the comment that there should be only two categories of changes but recognizes that the regulations should be revised to allow

more types of changes to be implemented in 30 days. An important objective of this rulemaking is to provide for the prompt implementation of changes while allowing FDA to ensure that the changes do not have an adverse effect on the safety or effectiveness of the product. As proposed, §§ 314.70(g)(2) and 601.12(c) would have provided for the distribution of a product made using certain changes 30 days after notification to FDA but they did not provide for the full evaluation and approval by FDA of information gathered by the applicant in validating the change. As a consequence, under the proposed rule, FDA would have been unable to determine, because of the absence of data, that many changes could be considered to have a moderate, rather than a substantial, potential to have an adverse effect on the safety or effectiveness of the product.

Accordingly, FDA is revising proposed §§ 314.70(g)(2) and 601.12(c) to require, for changes which have a moderate potential to have an adverse effect on the safety or effectiveness of the product, the submission of a supplement, rather than a notification, 30 days before distribution of the product made using the change. FDA is taking this initiative so that significantly more types of changes may be moved from the prior approval category, thereby allowing distribution of the product at or near the time of submission.

In this regard, in preparing this final rule, FDA reviewed those changes that were identified in the proposed rule (and discussed in the draft guidance documents) as subject to supplement submission and FDA approval prior to distribution of the product made using the change. The agency determined that for many of these changes, agency review of the data is necessary to assess any potential long-term effect on the continued safety or effectiveness of the product, but that it is unnecessary to require that FDA approval of the supplement be obtained before the product made using the change is initially distributed. In addition, as discussed previously in this document, FDA has decided to permit the use of a ''comparability protocol'' for certain changes in lieu of requiring supplement submission and approval prior to distribution of the particular product made using the change. Thus, as described in the guidance documents being made available with this final rule, a change that is usually considered to have a substantial potential to have an adverse effect on the safety or effectiveness of the product may, in certain circumstances, be implemented and the product distributed not less than 30 days after FDA's receipt of the supplement or, in some cases, immediately upon submission of the supplement notifying the agency of the change, provided the change has been evaluated by the applicant in accordance with an FDA approved comparability protocol. The supplement is then reviewed by FDA to assure that there is adequate evidence that the change will consistently result in a safe and effective product. As provided in §§ 314.70(g)(2)(iii) and 601.12(c)(3) of the final rule, the information to be submitted would be the same type of information as is required for a supplement subject to approval by FDA prior to distributing the product made using the change.

In the guidance documents being made available elsewhere in this issue of the **Federal Register**, FDA identifies a number of additional types of changes which, under its current interpretation of the rule, may be implemented 30 days after receipt by FDA of the supplement, but for which FDA approval before implementation would have been required under the proposed rule. In addition, the final rule provides that, for some other types of changes, implementation can occur immediately upon submission of the supplement to FDA. The reduction in delays gained by reducing the number of types of changes subject to supplement submission and prior approval by FDA before distribution of the product made using the change, and from the use of comparability protocols, can only be achieved if FDA has the opportunity to evaluate the information in the form of a supplement to assure that there is no long-term potential that the change or many sequential changes made over time may have an adverse effect on the product.

Potential applicants should be aware that complete review and approval of a supplement will take longer than 30 days. There may be instances where FDA determines, after the product made using the change has been distributed, that the information submitted in the supplement fails to adequately demonstrate the continued safety or effectiveness of the product made using the change. In such cases, FDA will make all possible efforts to resolve problems with the applicant concerning the supplement submission without requiring removal of the product from the marketplace. In assessing an applicant's plans to correct a problem, the agency intends to consider the applicant's reasons for making the change and the available alternatives to the change. In cases where FDA determines that there may be a danger to public health due to the continued marketing of the product, or when FDA determines that the issues may not otherwise be resolved, the agency may require that the applicant cease distribution of the product made using the change or that the product be removed from distribution pending resolution of the issues related to the change.

8. One comment on proposed § 601.12(b)(2)(vi) (§ 601.12(b)(3)(vi) in the final rule) recommended that an applicant have the option of providing a detailed summary of the validation protocol and data, and the agency could request copies of the entire protocol and all data, if needed.

FDA disagrees with the comment. FDA believes that submission of the complete validation protocol and data is necessary to assure that FDA may fully evaluate any variability in test results that might not be apparent in a summary of test results. The agency has frequently encountered instances in which the average of the test results was within acceptable limits but variability in test results indicated a problem with the reproducibility of the test or demonstrated variability in product quality. In order to understand the implications of any such variability, it is necessary to review all data and the complete validation protocol specifying the test methodology used.

9. One comment recommended that only one supplement to a product license application should be necessary to implement a change by all facilities under a single establishment license.

This rulemaking does not address the overall licensing policies of the agency. In a related initiative, FDA is reviewing licensing policies and regulations. FDA will consider the comment in its general review of licensing policies and intends to publish additional documents in the **Federal Register** regarding licensing policies.

10. One comment on proposed § 601.12(c) suggested that the requirement for notification to FDA not less than 30 days prior to distributing the product be expanded to include a subcategory for permitting the notification of FDA concurrent with the distribution of the product made using the change.

FDA agrees with the comment. FDA believes 30 days is often necessary to assure that the supplement is complete and that the change qualifies for the moderate potential category. However, in other cases, such as when the change has been evaluated in accordance with an approved comparability protocol, or

where a change is one which in the agency's experience has always been reported by applicants in the correct category, and with the proper documentation, a change may be implemented immediately upon submission of the supplement. Accordingly, FDA is adding §§ 314.70(g)(2)(v) and 601.12(c)(5) in the final rule to provide that FDA may, for certain changes otherwise requiring submission of a supplement at least 30 days prior to distribution of the product made using the change, permit the distribution of the product to begin immediately upon receipt of the supplement by the agency. Such types of changes may be made in connection with approved comparability protocols or may be discussed in guidance documents.

11. One comment on proposed § 601.12(c) noted that the proposed rule did not specify the manner by which FDA would notify an applicant of its determination of whether the notification was accepted or if additional information was needed. The comment recommended that FDA establish a maximum time period, such as 21 days, after which the applicant can be assured that no request for significant information is forthcoming, thus allowing the applicant to begin marketing the product 30 days after submission with confidence that FDA has no objection.

As discussed earlier in this document, the final rule has replaced the ''notification'' with a supplement which may be implemented in 30 days. During the 30-day period from the date of receipt of a supplement, FDA will perform a preliminary review of the supplement to determine whether it is complete and whether the type of change qualifies under §§ 314.70(g)(2)(iv) or 601.12(c)(4) for distribution of the product made using the change 30 days after receipt of the supplement. The means of notifying the applicant of whether the supplement has been accepted as a ''30-day supplement'' depends on the individual circumstances surrounding the supplement. FDA recognizes that when there are problems with the supplement that may delay product distribution, the applicant should be notified as quickly as possible. Official notification will be by letter. To notify the applicant that the supplement has been received, FDA will send an acknowledgment letter assigning a reference number to the supplement.

Although FDA intends to perform this preliminary review as expeditiously as possible, there may be some cases where the entire 30-day period is necessary to determine if the supplement is complete and qualifies for implementation 30 days after submission. It is the responsibility of the applicant to determine whether it should prepare to release the product 30 days after submission of the supplement, recognizing that the release may be delayed because of deficiencies in the supplement, or make other arrangements to better accommodate such a possibility.

12. In the preamble to the proposed rule, FDA requested comments as to whether the information to be included in an annual report under existing § 314.81(b)(2), currently applicable to nonbiological new drugs, should be applied to licensed biological products. One comment expressed the opinion that the information required under § 314.81(b)(2) is more onerous than the proposed requirements in § 601.12(d) and should not be applied. Another comment stated that the information required by § 314.81(b)(2) has little relevance to blood and plasma establishments.

FDA requested comment to determine if applicants who manufacture both drugs and biological products preferred that the required content of the annual reports for drugs and biologics be identical. Only two comments were received in response to the agency request and both opposed complete harmonization. The agency is committed to harmonizing reporting requirements for drugs and biologics as much as possible and will continue to evaluate the need for identical content in annual reports. However, based on comments received, FDA has determined that it would be appropriate to harmonize the requirements for the annual report as they relate only to manufacturing changes at this time. The final rule at § 314.70(g)(3) references the annual report requirements for drugs approved under a new drug application (NDA) for products subject to § 314.70(g). For biological products, the language in § 601.12(d)(2)(i) through (d)(2)(vii) will require the same type and amount of information for manufacturing changes as is required under § 314.81(b)(iv)(b). This harmonizes the reporting requirements as they relate to postapproval changes for drugs and biologics without adding, for biological products, the additional requirements for other information required in an annual report for a drug approved under an NDA. The full description of the changes would include pertinent data from studies and tests performed to evaluate the effect of the change on the safety and effectiveness of the product. This differs from the proposed rule and is now appropriate because more changes that previously required submission of a supplement to FDA under the proposed rule will now require only the submission of an annual report. These data will allow the agency to help assess the impact of numerous changes that may occur to a product over time.

13. One comment on proposed § 601.12(d) asked whether the annual report should include a description of all changes or only those not otherwise reported to FDA under the proposed regulations.

The annual report should include information concerning only those changes that have not previously been reported to FDA in a supplement.

FDA recognizes the need to avoid redundant reporting of changes. Some products, particularly blood and blood components, are closely related and a single change may affect multiple products. Under the proposed rule, a minor change, which has a minimal potential to have an adverse effect on the safety or effectiveness of the product, would be reported in the annual report for each affected product on or about the first anniversary date of the approval of the application for the product. In § 601.12(d)(1) of the final rule, FDA is adding a provision to permit an applicant to request an alternative date for submission of an annual report so that multiple reports may be combined into a single combined annual report submission.

14. One comment on proposed § 601.12(d) asked for a clarification as to whether the annual report should include facility changes of the type previously contained in an establishment license application but for which FDA no longer requires submission in an application for a specified biotechnology product (see the final rule published in the **Federal Register** of May 14, 1996 (61 FR 24227)).

If the change relates to a matter which, under current procedures, would not be described in an original application and its supplements, reporting of the change is not required.

15. Two comments on proposed § 601.12(e) (§ 601.12(f) in the final rule) recommended that § 601.12(e)(4) be replaced by a cross-reference to § 314.70 so that all changes to advertising and promotional labeling for drug and biological products would be covered by one set of regulations. One additional comment recommended that proposed § 601.12(e) cross-reference § 314.70 for labeling changes and recommended that proposed § 601.12(e)(4) regarding advertisements and promotional

labeling replace existing § 601.45 (21 CFR 601.45).

Section 601.45 applies only to promotional materials relating to biological products intended for serious or life-threatening illness being considered for accelerated approval. FDA believes these requirements continue to be necessary for biological products being considered for accelerated approval.

FDA considered consolidating the requirements for advertising and labeling for drugs and biologics under one set of regulations but decided that the regulations are more useful if all requirements applicable to the reporting of changes to a license of a biological product are directly or indirectly included in one separate set of regulations. Advertisements and promotional labeling for both licensed biological products and drug products with approved NDA must be reported in accordance with the same requirements of § 314.81(b)(3), except that, as discussed previously in this document, different forms will be used until the final revised harmonized form is available.

16. One comment on proposed § 601.12(e)(2)(i)(D) (§ 601.12(f)(2)(i)(D) in the final rule), noted that to submit a labeling change to ''delete false, misleading, or unsupported indications for use or claims for effectiveness'' would be equivalent to acknowledging that the product has been misbranded. The comment asked for examples of when there might be circumstances when FDA would have previously approved a label that so misbranded the product.

Although this type of labeling change is infrequent, it has occurred in the past. For example, analyses of the results of postapproval studies may show that information included in the approved labeling is false or unsupported. Occasionally, an applicant may discover after approval of the product that data obtained from the clinical or laboratory studies sponsored by the applicant contained false information or, upon reevaluation, does not support claims made in the labeling. Also, the applicant may determine that persons using the product are making incorrect inferences from wording in the labeling and wording changes are necessary to ensure that the product is not used inappropriately. Changes made in the above instances would be reported in accordance with § 601.12(f)(2)(i)(D).

17. One comment recommended the deletion of § 610.9 because it is redundant with provisions in the proposed rule.

FDA disagrees with the comment but believes that the relationship among § 610.9, a similar regulation in § 640.120, and the regulations in the final rule should be clarified. Section 610.9 provides procedures for a manufacturer of a biological product to modify a particular test method or manufacturing process, which is specified in the biologics regulations upon demonstrating to FDA that the modification will provide assurances of the effects on the safety and effectiveness of the biological product equal to or greater than the test method or process specified in the regulations. Section 640.120 provides procedures for licensed and unlicensed manufacturers of blood, blood components, and blood products to obtain FDA approval for an exception or alternative to any requirement in part 640 (21 CFR part 640), subchapter F. Sections 610.9 and 640.120 are intended to provide flexibility for an applicant to obtain FDA approval of a change to a test method, manufacturing process, or other requirement from that specified in the regulations.

Section 601.12 of the final rule provides for the reporting of changes, including those for which approval under §§ 610.9 or 640.120 is required. In some cases, a change requiring approval under §§ 610.9 or 640.120 may be eligible for distribution 30 days after FDA's receipt of the supplement requesting approval of the change. Accordingly, FDA is amending §§ 610.9 and 640.120 in the final rule to clarify that FDA may permit changes submitted under § 610.9 or changes submitted by licensed establishments under § 640.120 to be distributed as provided in §§ 601.12(b) and (c) of the final rule.

FDA is also taking this opportunity to amend § 610.9 to clarify that a request for approval of an equivalent method or process can be submitted either as part of the original application (or as an amendment to the original, pending application) or as a supplement to the approved application. Section 610.9 previously specified that the request should be submitted as a license supplement.

18. One comment urged that CBER continue to be directly involved in inspections of well-characterized biotechnology products so that the agency may provide proper scientific review and oversight of those changes not reported before product distribution.

FDA agrees that appropriate scientific oversight should be given to help assure the continued safety and effectiveness of the products, particularly when there is a significant change in a method of manufacture. The agency will consider the comment when reviewing its overall inspectional policies.

19. One comment recommended that the review and regulation of all well-characterized biotechnology products be consolidated into one office serving both CDER and CBER.

This comment is outside the scope of this final rule. FDA is not considering such a reorganization at this time.

20. One comment recommended deletion of parts 610 through 680 (21 CFR parts 610 through 680) because these requirements are more appropriately addressed in approved marketing applications, compendia, and guidance documents.

In the **Federal Register** of August 1, 1996 (61 FR 40153), FDA issued a final rule removing the regulations in parts 620, 630, and 650 in their entirety and removing sections of parts 610, 640, 660, and 680. The remaining regulations continue to be under review within the agency and FDA intends to pursue additional rulemaking at a later date proposing to retain, revise, or remove many of the remaining regulations.

21. One comment from a licensed blood establishment recommended that a product license application supplement not be required for a change relating to a device which has received 510(k) clearance from FDA. The comment noted that the applicant should be permitted to implement the change with concurrent notification.

FDA disagrees with the comment. On occasion, a licensed blood establishment may change the type of equipment used in the collection or processing of blood and blood components. For example, a blood establishment may decide to change from using manual pheresis equipment for the collection of Source Plasma or other blood components to automated equipment which has already been cleared for such use as a medical device, either with an approved premarket approval application or cleared as substantially equivalent under section 510(k) of the act (21 U.S.C. 360(k)). The purpose of the supplement to the product license application is to assure that the use of the equipment has been properly validated at the blood establishment, that the persons using the equipment have been properly trained, and that appropriate standard operating procedures are in place to assure the safety of the donors from whom the blood components will be collected. FDA believes that a change from manual to automated pheresis equipment that is not properly implemented may have a substantial potential to have an adverse effect on the health of the donors as well as on

the safety and effectiveness of the products being collected. For this reason, FDA believes that a supplement submission to convert from manual to automated pheresis equipment should be subject to approval by FDA before the change is implemented. FDA notes that for certain other types of similar changes, such as changing from one type of automated equipment to another, there is less potential for an adverse effect and the product made using the change may be distributed 30 days after receipt by FDA of the supplement reporting the change.

22. One comment recommended that FDA not set specific requirements for submission of changes to a pending application. This flexibility could help expedite the approval of life-saving products, such as a new treatment for cancer.

Former § 601.12 applied both to changes to an approved application and to changes to a pending application. In the preamble to the proposed rule (61 FR 2739 at 2742), FDA announced its intention to consider whether it is appropriate to issue specific requirements for submitting amendments to pending license applications as part of its review of licensing requirements. The review of licensing requirements continues; however, FDA recognizes that its regulations and policies must provide adequate flexibility to accommodate the wide variety of products which are subject to licensure.

The agency has already taken a number of steps to ensure the expeditious review and approval of important new drugs and biologics, including a commitment under the Prescription Drug User Fee Act of 1992 (Pub. L. 102–571) to endeavor to complete the review of applications for ''breakthrough'' drugs and biologics within certain specified timeframes. Efforts to improve the system for the review and approval of important new drugs and biological products are continuing.

23. One comment requested that FDA discontinue its policy of requiring submission of plateletpheresis products for quality control testing as a prerequisite for license approval for such products.

The comment is beyond the scope of this rulemaking, which deals with the procedures for the reporting of changes to a license application. FDA notes, however, that for the present time, the agency plans to continue its practice of performing quality control testing as part of its review of a license application relating to a plateletpheresis product. Plateletpheresis is a sophisticated process, requiring considerable expertise to perform properly. In recent quality control testing, performed in 1996, FDA found that 26 of 279 samples submitted did not meet appropriate specifications. Results from additional samples indicated problems with pheresis procedures. See § 640.25(b) for additional standards regarding quality control testing. Because of this relatively high rate of failure, FDA believes that continued quality control testing by the agency is necessary to assure the continued safety and effectiveness of plateletpheresis products.

24. One comment recommended that FDA provide an applicant with a specific, detailed, written explanation for finding a license ''not approvable'' and that compliance deficiencies unrelated to the change specified in the application should not justify a ''not approvable'' decision.

The comment is beyond the scope of this rulemaking, which deals with the procedures for the reporting of changes. The entire licensing process, including the review and approval of license supplements, continues to be under review within FDA. This comment will be considered by the agency as part of its review of the licensing process.

25. One comment recommended that the final rule be made effective immediately upon its publication to provide immediate relief from excess reporting burdens.

FDA agrees the final rule should be implemented as soon as possible. Additional information regarding effective dates and other implementation issues is presented at the end of this preamble.

26. One comment on the ''Analysis of Impacts'' section of the preamble of the proposed rule noted that the analysis did not specify how many establishments were involved and whether the proposed regulations would truly result in a paperwork reduction. The comment requested that FDA describe more clearly the expected reduction in paperwork burdens.

The ''Analysis of Impacts'' sections of the proposed and final rules are based on an evaluation of those supplements submitted to FDA under the previous regulations during a specified time period. All applicants holding licenses for biological products or an NDA for those biotechnology products affected by § 314.70(g) are potential respondents. The analysis is based on the number of supplements submitted in the recent past which would, under the final rule, be subject to each form of reporting to FDA. From the burden hours associated with each of the possible means of reporting to FDA, assuming the types of changes occurring under the final rule are comparable to those which were evaluated, the estimated change in costs to the applicant can be readily calculated.

FDA notes that the decrease in paperwork is only part of the relief from regulatory burdens achieved by the final rule. Under the new regulations many changes may be implemented more expeditiously and the product marketed more quickly. FDA believes this ability to readily market a product made with improved technology or improved labeling will be of considerable economic benefit to the applicant and the public. Because these benefits are indirect benefits, FDA does not have the information necessary to quantify the economic benefits associated with such timely marketing of products.

V. Effective Dates and Other Implementation Issues

The final rule is effective October 7, 1997. On or after that date, FDA will accept supplements submitted in accordance with the final rule. For supplements which have already been submitted to FDA and which are pending approval, the applicant should notify FDA as to whether it believes: (1) The supplement continues to be subject to approval by FDA before implementation of the change; (2) the change may be implemented but is subject to FDA approval as a supplement; or (3) the supplement should be withdrawn because review of the change as a supplement is no longer necessary and the change may be implemented and reported in an annual report. FDA will inform the applicant within 30 days of its receipt of this notification if it is not in agreement with the applicant's assessment.

FDA is requesting the submission of the initial annual report required by §§ 314.70(g)(3) and 601.12(d) and (f)(3) within 60 days of the first anniversary date of the approval of the application of the product occurring on or after January 20, 1998. For products with an earlier anniversary date, the annual report shall be submitted within 60 days of the next anniversary date and should report all applicable changes occurring since the time of issuance of the final rule.

VI. Analysis of Impacts

A. Review Under Executive Order 12866 and the Regulatory Flexibility Act

FDA has examined the impact of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612). 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 impact; and equity). The agency believes that this final rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the final rule is a significant regulatory action as defined by the Executive Order and is subject to review under the Executive Order because it deals with a novel policy issue.

In accordance with the principles of Executive Order 12866, the overall result of the final rule will be a substantial reduction in burdens on applicants seeking approval of a product subject to this rule. FDA anticipates that the final rule will facilitate an applicant's ability to market a product improved by a change in manufacturing or labeling without unnecessary delays while reducing the overall paperwork burden associated with reporting such a change to FDA. In addition, FDA anticipates that the final rule may encourage applicants to improve their licensed products, product labeling, and methods of manufacture.

Unless the head of the agency certifies that the rule does not impose a significant impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant economic impact of a rule on small entities. The final rule will reduce the overall burdens associated with reporting changes in manufacturing and labeling of licensed biological products. It also provides increased flexibility for applicants in selecting the means of reporting manufacturing changes by providing for the use of a comparability protocol through which the agency may determine that the change has a decreased potential for an adverse effect on the safety and effectiveness of the product when compared with the potential generally associated with that type of change. In many cases under the final rule, an applicant will be able to market a product made using a change in manufacturing more rapidly than previously permitted under the regulations.

Because, as stated above, the overall result of the final rule will be a substantial reduction in the regulatory and reporting burdens, the Commissioner of Food and Drugs certifies that the final rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

Although no further analysis is required, in developing this final rule, the agency did consider the impact of the rule on small entities. The agency also considered various regulatory options to maximize the net benefits of the rule to small entities without compromising the agency's ability to assure the continued safety and effectiveness of the products to which the rule applies. The following analysis briefly examines the potential impact of the final rule on small businesses.

1. The Need for the Regulation

The purpose of the final rule is to amend the regulations for reporting to FDA changes to an approved application for a biological product in order to reduce unnecessary reporting burdens on applicants holding approved licenses to manufacture biological products and on applicants with an approved NDA for specified biotechnology products. FDA issued the proposed rule as part of its response to several mandates to reduce the burdens associated with government regulation, while assuring the continued safety and effectiveness of regulated products.

The final rule takes into account comments submitted to the Dockets Management Branch, and discussions and information obtained through public participation in the public meeting held on April 19, 1996, to discuss and gather information and views on the proposed rule and two draft guidance documents. The objective of the final rule is to harmonize regulations administered by CDER and CBER in FDA, to reduce unnecessary burdens, and improve the consistency in the processes for complying with FDA's regulations without diminishing public health protection.

As stated previously, FDA held an open public meeting during the comment period to facilitate public comment on this rule. FDA is announcing the availability of final guidance documents, revised from those proposed as a result of public comment, which are intended to aid applicants in complying with the requirements of this final rule.

2. Description of Requirements

Any applicant holding an approved marketing application for a licensed biological product or specified biotechnology product will be required to report a change in the approved manufacturing process or in labeling by the appropriate procedure described in this final rule. The rule applies both to small and large for-profit business entities, and to small and large nonprofit organizations.

The agency believes the regulation is flexible and is consistent with contemporary standards. Because this final rule represents a decrease in reporting burdens and other economic burdens previously applicable to the same products, FDA believes that firms should have no problem with complying with these regulations. No particular professional skills are needed to assemble the information to be reported to FDA.

3. Types and Number of Firms Affected

Approximately 400 firms are affected by this final rule. Approximately half, primarily establishments with licenses for blood and blood component products, are nonprofit institutions. The remainder are large for-profit businesses.

4. Alternatives

A number of alternatives were considered in preparing this final rule. Each alternative was evaluated as to its adequacy in providing in a timely way the information needed for FDA to assure the continued safety and effectiveness of the affected products, and evaluated with regard to burdens related to paperwork and the applicant's ability to market a product made with a changed manufacturing process or distributed with revised labeling. The agency decided not to provide different reporting requirements for small businesses because such an alternative would threaten the continued safety and effectiveness of products marketed by small businesses. For all applicants, regardless of size, the agency believes it has selected the reporting alternatives which impose the minimum burdens upon the applicants while assuring the continued safety and effectiveness of the affected products.

5. Response to Comments

Only one comment was received concerning the Regulatory Flexibility Analysis provided in the proposed rule. The comment asked for further clarification regarding the projected reduction in burdens associated with the revised regulations. Most of the reduction in paperwork burdens, now projected as a 10 percent reduction, is associated with the fact that some changes which previously were subject to submission of a supplement and approval by FDA prior to distribution of the product made using the change may now be reported in an annual report

with a significant reduction in the information that is to be submitted. Considerable reduction in economic burdens is expected to result from the flexibility included in the final rule to permit the distribution of a product made using a change by the most timely means possible while assuring the continued safety and effectiveness of the product. Because FDA has no data to relate time saved in marketing a product with the resulting economic benefit, FDA cannot offer a monetary estimate of the savings at this time.

B. Review Under the Paperwork Reduction Act of 1995

This final rule contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). The title, description, and respondent description of the information collection provisions are shown below with an estimate of the annual reporting burden. Included in the estimate is the time for reviewing instructions, gathering and maintaining the data needed, and completing and reviewing the collection of information.

Title: 21 CFR 601.12—Changes to an Approved Application and 21 CFR 314.70(g)—*Exception*.

Description: This final rule revises the requirements for respondents to report to FDA changes in the product, labeling, production process, equipment, quality controls facilities, or responsible personnel established in an approved application for a biological product or for a specified biotechnology product. The respondent will report a change to FDA in one of the three following ways depending on the potential for the change to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product: (1) Changes that have a significant potential to have an adverse effect on the product will be submitted in a supplement requiring prior approval by FDA before distribution of the product made using the change; (2) changes that have a moderate potential to have an adverse effect on the product will be submitted to FDA in a supplement not less than 30 days prior to distribution of the product made using the change unless FDA permits distribution upon its receipt of the supplement; and (3) changes that have a minimal potential to have an adverse effect on the product will be submitted by the respondent in an annual report.

Labeling changes for a biological product will also be submitted in one of the following ways: (1) A supplement requiring FDA approval prior to distribution of product with the revised labeling; (2) a supplement requiring FDA approval but permitting the distribution of the product with the accompanying revised labeling at the time the supplement is submitted; or (3) submission of final printed labeling in an annual report. Promotional labeling and advertising will be submitted in accordance with § 314.81(b)(3)(i). Labeling changes for biotechnology products regulated under the act but not under the PHS Act are not addressed in § 314.70(g) and will not be affected by this final rule. The agency is developing technology to permit the submission of the information required by this rule electronically. The agency anticipates that the use of electronic media will substantially further reduce the paperwork burden associated with these reporting requirements.

Description of Respondents: All manufacturers and applicants holding a biological license approved under section 351 of the PHS Act, and all manufacturers and applicants of specified biotechnology products holding an approved NDA.

Burden estimate: As mentioned in the proposed rule, FDA estimates that 20 percent of all reports required under these final regulations will be prepared by contractors. The burden hours for affected industry in the chart below therefore reflect a 20 percent reduction. It is estimated that a contractor will charge $40 per hour for the service of preparing these reports. The 20 percent burden hours multiplied by $40 per hour are reflected in the table, under the column labeled ''Operating and Maintenance Costs.''

The burden estimate for this final rule differs from the estimate given for the proposed rule (see 61 FR 2739 at 2745) in two important respects. First, FDA has revised §§ 314.70(g)(2) and 601.12(c) in the final rule to require submission of a supplement rather than a notification for changes that have a moderate potential to have an adverse effect on the safety or effectiveness of the product. This revision will result in an estimated 10 additional burden hours per submission (50 for a supplement versus 40 for a notification). Second, substantially more supplements concerning changes in manufacturing and labeling for biological products are being submitted than during the time period used to prepare the estimate in the proposed rule (an estimated 2,300 submissions in 1996 versus 1,550 submissions in 1994). Although this increase results from increased industry activity, not from any modification to the proposed rule, the burden estimate has been adjusted to reflect the increase.

ESTIMATED ANNUAL REPORTING BURDEN

21 CFR Section	Number of Respondents	Hours Per Response	Number of Responses	Number of Responses Per Respondent	Total Operating and Maintenance Costs	Total Hours Per Regulation
601.12(b)	391	80	900	2.3	$576,000	57,600
601.12(c)	391	50	720	1.8	$288,000	28,800
601.12(d)	391	10	120	0.3	$9,600	960
601.12(f)(1)	391	40	200	0.51	$64,000	6,400
601.12(f)(2)	391	20	20	0.05	$3,200	320
601.12(f)(3)	391	10	220	0.56	$17,600	1,760
601.12(f)(4)	391	10	110	0.28	$8,800	880
314.70(g)(1)	4	80	50	12.5	$32,000	3,200
314.70(g)(2)	2	50	3	1.5	$1,200	120
314.70(g)(3)	6	10	20	3.33	$1,600	160
TOTALS					$1,002,000	$100,200

There are no capital costs associated with this collection of information.

As required by section 3506(c)(2)(B) of the Paperwork Reduction Act of 1995 (the PRA), FDA provided an opportunity for public comment on the information collection provisions of the proposed rule. All comments received

agreed that FDA's proposal to modify the requirements for reporting changes to approved applications would reduce the burden to industry without diminishing public health protection. Even with the increase in burden in the final rule as compared with the proposed rule, FDA estimates that the modified reporting requirements will achieve a net burden reduction of approximately 10,000 hours per year.

As required by section 3507(d)(1)(A) of the PRA, FDA submitted the information collection provisions of the proposed rule to OMB. Although these provisions were approved, FDA has submitted the information collection provisions of the final rule to OMB for review because of the revised requirement to submit a supplement rather than a notification for changes that have a moderate potential to have an adverse effect on the safety or effectiveness of the product. Prior to the effective date of this final rule, FDA will publish a notice in the **Federal Register** of OMB's decision to approve, modify, or disapprove the information collection provisions in the final rule. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

C. Environmental Impact

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

List of Subjects

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.

21 CFR Part 610

Biologics, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 640

Blood, Labeling, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, and under the authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 314, 600, 601, 610 and 640 are amended as follows:

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

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

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 701, 704, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371, 374, 379e).

2. Section 314.70 is amended by adding a new paragraph (g) to read as follows:

§ 314.70 Supplements and other changes to an approved application.

* * * * *

(g) *Exception*. An applicant proposing to make a change of a type described in paragraphs (a), (b)(1), (b)(2), (c)(1), (c)(3), (d)(1), and (d)(4) through (d)(9) of this section affecting a recombinant DNA-derived protein/polypeptide product or a complex or conjugate of a drug with a monoclonal antibody regulated under the Federal Food, Drug, and Cosmetic Act shall comply with the following:

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

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

(A) Changes in the qualitative or quantitative formulation or other specifications as provided in the approved application or in the regulations;

(B) Changes requiring completion of an appropriate human study to demonstrate the equivalence of the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product;

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

(D) Changes in the source material or cell line;

(E) Establishment of a new master cell bank or seed; and

(F) Changes which may affect product sterility assurance, such as changes in product or component sterilization method(s) or an addition, deletion, or substitution of steps in an aseptic processing operation.

(iii) The applicant must obtain approval of the supplement from FDA prior to distribution of the product made using the change. Except for submissions under paragraph (g)(4) of this section, the following shall be contained in the supplement:

(A) A detailed description of the proposed change;

(B) The product(s) involved;

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

(D) A description of the methods used and studies performed to evaluate the 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;

(E) The data derived from such studies;

(F) Relevant validation protocols and data; and

(G) A reference list of relevant standard operating procedures (SOP's).

(2) *Changes requiring supplement submission at least 30 days prior to distribution of the product made using the change.* (i) A supplement shall be submitted for any change in the product, production process, quality controls, equipment, or facilities that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product. The supplement shall be labeled ''Supplement—Changes Being Effected in 30 Days'' or, if applicable under paragraph (g)(2)(v) of this section, ''Supplement—Changes Being Effected.''

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

(A) Change in the site of testing from one facility to another;

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

(C) Replacement of equipment with that of similar, but not identical, design and operating principle that does not affect the process methodology or process operating parameters.

(iii) Pending approval of the supplement by FDA, and except as provided in paragraph (g)(2)(v) of this section, distribution of the product made using the change may begin not less than 30 days after receipt of the supplement by FDA. The information listed in paragraph (g)(1)(iii)(A) through

(g)(1)(iii)(G) of this section shall be contained in the supplement.

(iv) If within 30 days following FDA's receipt of the supplement, FDA informs the applicant that either:

(A) The change requires approval prior to distribution of the product in accordance with paragraph (g)(1) of this section; or

(B) Any of the information required under paragraph (g)(2)(iii) of this section is missing; the applicant shall not distribute the product made using the change until FDA determines that compliance with this section is achieved.

(v) In certain circumstances, FDA may determine that, based on experience with a particular type of change, the supplement for such change is usually complete and provides the proper information, and on particular assurances that the proposed change has been appropriately submitted, the product made using the change may be distributed immediately upon receipt of the supplement by FDA. These circumstances may include substantial similarity with a type of change regularly involving a ''Supplement—Changes Being Effected'' supplement, or a situation in which the applicant presents evidence that the proposed change has been validated in accordance with an approved protocol for such change under paragraph (g)(4) of this section.

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

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

(A) Any change made to comply with an official compendium that is consistent with FDA requirements;

(B) The deletion of an ingredient intended only to affect the color of the product;

(C) An extension of an expiration date based upon full shelf life data obtained from a protocol approved in the application;

(D) A change within the container and closure system for solid dosage forms, based upon a showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium;

(E) A change in the size of a container for a solid dosage form, without a change from one container and closure system to another;

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

(G) The addition or deletion of an alternate analytical method.

(4) 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 product as they may relate to the safety or effectiveness of the product. Any such protocols, or change to a protocol, shall be submitted as a supplement requiring approval from FDA prior to distribution of the product which, if approved, may 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.

* * * * *

PART 600—BIOLOGICAL PRODUCTS: GENERAL

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

Authority: Secs. 201, 501, 502, 503, 505, 510, 519, 701, 704, of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 360i, 371, 374); secs. 215, 351, 352, 353, 361, 2125 of the Public Health Service Act (42 U.S.C. 216, 262, 263, 263a, 264, 300aa–25).

4. Section 600.3 is amended by adding new paragraphs (ff) and (gg) to read as follows:

§ 600.3 Definitions.

* * * * *

(ff) *Amendment* is the submission of information to a pending license application or supplement, to revise or modify the application as originally submitted.

(gg) *Supplement* is a request to the Director, Center for Biologics Evaluation and Research, to approve a change in an approved license application.

PART 601—LICENSING

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

Authority: Secs. 201, 501, 502, 503, 505, 510, 513–516, 518–520, 701, 704, 721, 801, of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 360c–360f, 360h–360j, 371, 374, 379e, 381); secs. 215, 301, 351, 352, of the Public Health Service Act (42 U.S.C. 216, 241, 262, 263); secs. 2–12 of the Fair Packaging and Labeling Act (15 U.S.C. 1451–1461).

6. Section 601.12 is revised to read as follows:

§ 601.12 Changes to an approved application.

(a) *General.* As provided by this section, an applicant shall inform 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). Before distributing a product made using a change, an applicant shall demonstrate through appropriate validation and/or other clinical and/or non-clinical 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.

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

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

(i) Changes in the qualitative or quantitative formulation or other specifications as provided in the approved application or in the regulations;

(ii) Changes requiring completion of an appropriate human study to demonstrate the equivalence of the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product;

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

(iv) Changes in the source material or cell line;

(v) Establishment of a new master cell bank or seed; and

(vi) Changes which may affect product sterility assurance, such as changes in product or component sterilization method(s), or an addition, deletion, or substitution of steps in an aseptic processing operation.

(3) The applicant must obtain approval of the supplement from FDA prior to distribution of the product made using the change. Except for

submissions under paragraph (e) of this section, the following shall be contained in the supplement:

(i) A detailed description of the proposed change;

(ii) The product(s) involved;

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

(iv) A description of the methods used and studies performed to evaluate the 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;

(v) The data derived from such studies;

(vi) Relevant validation protocols and data; and

(vii) A reference list of relevant standard operating procedures (SOP's).

(c) *Changes requiring supplement submission at least 30 days prior to distribution of the product made using the change.* (1) A supplement shall be submitted for any change in the product, production process, quality controls, equipment, facilities, or responsible personnel that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product. The supplement shall be labeled ''Supplement—Changes Being Effected in 30 Days'' or, if applicable under paragraph (c)(5) of this section, ''Supplement—Changes Being Effected.''

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

(i) Change in the site of testing from one facility to another;

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

(iii) Replacement of equipment with that of similar, but not identical, design and operating principle that does not affect the process methodology or process operating parameters.

(3) Pending approval of the supplement by FDA, and except as provided in paragraph (c)(5) of this section, distribution of the product made using the change may begin not less than 30 days after receipt of the supplement by FDA. The information listed in paragraph (b)(3)(i) through (b)(3)(vii) of this section shall be contained in the supplement.

(4) 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 product in accordance with paragraph (b) of this section; or

(ii) Any of the information required under paragraph (c)(3) of this section is missing; the applicant shall not distribute the product made using the change until FDA determines that compliance with this section is achieved.

(5) In certain circumstances, FDA may determine that, based on experience with a particular type of change, the supplement for such change is usually complete and provides the proper information, and on particular assurances that the proposed change has been appropriately submitted, the product made using the change may be distributed immediately upon receipt of the supplement by FDA. These circumstances may include substantial similarity with a type of change regularly involving a ''Supplement—Changes Being Effected'' supplement or a situation in which the applicant presents evidence that the proposed change has been validated in accordance with an approved protocol for such change under paragraph (e) of this section.

(d) *Changes to be described in an annual report (minor changes).* (1) Changes in the product, production process, quality controls, equipment, facilities, or responsible personnel that have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product shall be documented by the applicant in an annual report submitted each year within 60 days of the anniversary date of approval of the application. The Director, Center for Biologics Evaluation and Research, may approve a written request for an alternative date to combine annual reports for multiple approved applications into a single annual report submission.

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

(i) Any change made to comply with an official compendium that is consistent with FDA requirements;

(ii) The deletion 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 date based upon full shelf-life data obtained from a protocol approved in the application;

(iv) A change within the container and closure system for solid dosage forms, 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 of a container for a solid dosage form, without a change from one container and closure system to another;

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

(vii) The addition or deletion of an alternate analytical method.

(3) The following information for each change shall be contained in the annual report:

(i) A list of all products involved; and

(ii) A full description of the manufacturing and controls changes including: the manufacturing site(s) or area(s) involved; the date the change was made; a cross-reference to relevant validation protocols and/or SOP's; 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 they may relate to the safety or effectiveness of the product.

(4) The applicant shall submit the report to the FDA office responsible for reviewing the application. The report shall include all the information required under this paragraph for each change made during the annual reporting interval which ends on the anniversary date in the order in which they were implemented.

(e) 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 product as they may relate to the safety or effectiveness of the product. Any such protocols, or change to a protocol, shall be submitted as a supplement requiring approval from FDA prior to distribution of the product which, if approved, may 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) *Labeling changes.* (1) Labeling changes requiring supplement submission—FDA approval must be obtained before distribution of the product with the labeling change. Except as described in paragraphs (f)(2) and (f)(3) of this section, an applicant shall submit a supplement describing a proposed change in the package insert, package label, or container label, and include the information necessary to

support the proposed change. The supplement shall clearly highlight the proposed change in the labeling. The applicant shall obtain approval from FDA prior to distribution of the product with the labeling change.

(2) *Labeling changes requiring supplement submission—product with a labeling change that may be distributed before FDA approval.* (i) An applicant shall submit, at the time such change is made, a supplement for any change in the package insert, package label, or container label 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 abuse, dependence, psychological effect, or overdosage;

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

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

(ii) Pending approval of the supplement by FDA, the applicant may distribute a product with a package insert, package label, or container label bearing such change at the time the supplement is submitted. The supplement shall clearly identify the change being made and include necessary supporting data. The supplement and its mailing cover shall be plainly marked: ''Special Labeling Supplement—Changes Being Effected.''

(3) *Labeling changes requiring submission in an annual report.* (i) An applicant shall submit any final printed package insert, package label, or container label incorporating the following changes in an annual report submitted to FDA each year as provided in paragraph (d)(1) of this section:

(A) Editorial or similar minor changes; and

(B) A change in the information on how the product is supplied that does not involve a change in the dosage strength or dosage form.

(ii) The applicant may distribute a product with a package insert, package label, or container label bearing such change at the time the change is made.

(4) *Advertisements and promotional labeling.* Advertisements and promotional labeling shall be submitted to the Center for Biologics Evaluation and Research in accordance with the requirements set forth in § 314.81(b)(3)(i) of this chapter, except that Form FDA–2567 (Transmittal of Labels and Circulars) or an equivalent form shall be used.

(g) *Failure to comply.* In addition to other remedies available in law and regulations, in the event of repeated failure of the applicant to comply with this section, FDA may require that the applicant submit a supplement for any proposed change and obtain approval of the supplement by FDA prior to distribution of the product made using the change.

(h) *Administrative review.* Under § 10.75 of this chapter, an applicant may request internal FDA review of FDA employee decisions under this section.

PART 610—GENERAL BIOLOGICAL PRODUCTS STANDARDS

7. The authority citation for 21 CFR part 610 continues to read as follows:

Authority: Secs. 201, 501, 502, 503, 505, 510, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 371); secs. 215, 351, 352, 353, 361 of the Public Health Service Act (42 U.S.C. 216, 262, 263, 263a, 264).

8. Section 610.9 is revised to read as follows:

§ 610.9 Equivalent methods and processes.

Modification of any particular test method or manufacturing process or the conditions under which it is conducted as required in this part or in the additional standards for specific biological products in parts 620 through 680 of this chapter shall be permitted only under the following conditions:

(a) The applicant presents evidence, in the form of a license application, or a supplement to the application submitted in accordance with § 601.12(b) or (c), demonstrating that the modification will provide assurances of the safety, purity, potency, and effectiveness of the biological product equal to or greater than the assurances provided by the method or process specified in the general standards or additional standards for the biological product; and

(b) Approval of the modification is received in writing from the Director, Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448.

PART 640—ADDITIONAL STANDARDS FOR HUMAN BLOOD AND BLOOD PRODUCTS

9. The authority citation for 21 CFR part 640 continues to read as follows:

Authority: Secs. 201, 501, 502, 503, 505, 510, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 371); secs. 215, 351, 352, 353, 361 of the Public Health Service Act (42 U.S.C. 216, 262, 263, 263a, 264).

10. Section 640.120 is amended by revising paragraph (a) to read as follows:

§ 640.120 Alternative procedures.

(a) The Director, Center for Biologics Evaluation and Research, may approve an exception or alternative to any requirement in subchapter F of chapter I of title 21 of the Code of Federal Regulations regarding blood, blood components, or blood products. Requests for such exceptions or alternatives shall ordinarily be in writing. Licensed establishments shall submit such requests in accordance with § 601.12 of this chapter. However, in limited circumstances, such requests may be made orally and permission may be given orally by the Director. Oral requests and approvals must be promptly followed by written requests and written approvals.

* * * * *

Dated: May 27, 1997.

William B.Schultz,

Deputy Commissioner for Policy.

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