(3) The term ''product license application,'' as it is used in those sections of parts 600 through 680 of this chapter that are applicable to well-characterized biotechnology products, shall include a biologics license application for a well-characterized biotechnology product.

(4) To the extent that the requirements in this paragraph conflict with other requirements in this subchapter, this paragraph (c) shall supercede such other requirements.

Dated: January 8, 1996.

William B. Schultz,

Deputy Commissioner for Policy.

[FR Doc. 96–1582 Filed 1–25–96; 10:42 am]

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21 CFR Parts 314, 600, and 601

[Docket No. 95N–0329]

RIN 0910–AA57

Changes to an Approved Application

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend the biologics regulations for reporting changes to an approved application in order to reduce unnecessary reporting burdens on applicants holding licenses approved in 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 proposing to amend the corresponding drug regulations for submitting supplements for and reporting changes to an application approved under the Federal Food, Drug, and Cosmetic Act (the act) for well-characterized biotechnology products reviewed in the Center for Drug Evaluation and Research (CDER) to harmonize the drug and biologics regulations. These actions are part of FDA's continuing effort to achieve the objectives of the President's ''Reinventing Government'' initiatives.

DATES: Written comments on this proposed rule by April 29, 1996. Submit written comments on the information collection requirements by February 28, 1996, but not later than March 29, 1996. The agency proposes that any final rule that may issue based on this proposal become effective immediately upon its date of publication in the Federal Register.

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

FOR FURTHER INFORMATION CONTACT:

Tracey H. Forfa or Timothy W. Beth, 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–820), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–3510.

SUPPLEMENTARY INFORMATION:

I. Introduction

A. Background

This proposed rule is issued in accordance with the principles set forth in the Regulatory Flexibility Act of 1990 (Pub. L. 96–354), Executive Order 12866; the President's memorandum of March 4, 1995, announcing the ''Regulatory Reinvention Initiative;'' the President's memorandum of April 21, 1995, entitled, ''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.'' The Regulatory Flexibility Act requires Federal agencies to consider the burden a rule may have on small business entities through a regulatory flexibility analysis and to periodically review its rules to determine if regulatory burdens may be reduced. Executive Order 12866 directs Federal agencies and the Office of Information and Regulatory Affairs (OIRA) to implement measures that will reform and make the regulatory process more efficient.

Under Executive Order 12866, FDA published a document in the Federal Register on January 20, 1994 (59 FR 3043), that announced FDA's plan to review and evaluate all significant regulations for their effectiveness in achieving public health goals and in order to avoid unnecessary regulatory burden. FDA published two documents in the Federal Register of June 3, 1994 (59 FR 28821 and 28822), that announced the review of certain general biologics and blood and blood product regulations by CBER to identify those regulations that are outdated, burdensome, inefficient, duplicative, or otherwise unsuitable or unnecessary.

The President's memorandum of March 4, 1995, entitled ''Regulatory Reinvention Initiative'' sets forth four steps toward regulatory reform, one of which instructs agencies to revise those regulations that are in need of reform. FDA believes that this proposed regulation is in keeping with these principles without compromising the agency's duty and commitment to protect the public health. The President's memorandum of April 21, 1995, directs Federal agencies to reduce the frequency of regularly scheduled reports that the public is required, by rule or policy, to provide to the Federal government. In addition, the November 1995, Presidential National Performance Review report entitled ''Reinventing the Regulation of Drugs Made From Biotechnology,'' focused on FDA's efforts to reform the regulation of biotech drugs used for therapy.

FDA also held a public meeting on January 26, 1995, to discuss the retrospective review effort. The public meeting was a forum for the public to voice its comments regarding the retrospective review of regulations being undertaken by CBER.

Many of the comments submitted to the public docket regarding the CBER retrospective regulations review were requests to revise § 601.12 *Changes to be reported* (21 CFR 601.12). Most of those comments requested revision of the regulation to reduce the burden on applicants of reporting changes to an approved application. As part of the CBER regulatory review initiative, and in response to the comments received, FDA published in the Federal Register of April 6, 1995 (60 FR 17535), a document entitled, ''Changes to Be Reported for Product and Establishment License Applications; Guidance.'' The guidance document set forth FDA's current interpretation of § 601.12 and was intended to reduce the reporting burden as well as facilitate the timely implementation of certain changes by manufacturers. The guidance document was the first step in a reinventing Government initiative outlined in the April 1995 publication ''Reinventing Drug and Medical Device Regulations.''

Concurrently, CBER's Office of Blood Research and Review (OBRR), in letters to applicants and an industry trade organization and in presentations at a January 30 and 31, 1995, ''Licensing Blood Establishments'' workshop,

communicated FDA's interpretation of § 601.12 as it applies to blood establishments. OBRR discussed categories of changes that blood establishments could implement without supplement submission and FDA approval. These categories include noncritical standard operating procedures, certain personnel changes, and some facility changes. During a 9-month period (October 1994 to June 1995), CBER received over 850 such submissions that were not required to await FDA approval.

The agency is proposing to revise § 600.3 (21 CFR 600.3) and § 601.12 to permit more substantial report reduction as the second step in the President's reinvention initiative. FDA is also proposing to add § 314.70(g) (21 CFR 314.70(g)) which would apply to well-characterized biotechnology products approved under the act to harmonize CDER and CBER postapproval reporting requirements. FDA published a definition of a well-characterized therapeutic recombinant deoxyribonucleic acid (DNA)-derived and monoclonal antibody biotechnology product in a document published in the Federal Register of December 8, 1995, (60 FR 63048), as follows:

A chemical entity(ies) whose identity, purity, impurities, potency, and quantity can be determined and controlled.

Identity:

a. *Recombinant DNA Biotechnology Products*

The primary structure is known (i.e., amino acid sequence), and

The secondary structure is known (e.g., disulfide linkage), and

Post-translational modifications are known (e.g., glycosylation), or

b. *Monoclonal Antibodies*

The identity can be determined by rigorous physicochemical and immunochemical characterization without fully knowing its chemical structure

Purity and impurities:

The purity is quantifiable.

The impurities are quantifiable, and identified if feasible

Potency and quantity:

The biological activity is measurable.

The quantity is measurable.

Well-characterized therapeutic recombinant DNA-derived or monoclonal antibody biotechnology product require proper raw materials controls, process validation and controls, and sensitive and validated test methods and specifications.

FDA plans to hold an open public meeting that will be announced in a future issue of the Federal Register during the comment period of this proposed rule to facilitate public discussion.

B. Summary of the Proposed Rule

1. Summary of Changes to § 600.3—Definitions

There has been much confusion regarding the use of the words ''supplement'' and ''amendment'' in relation to license applications for biological products approved under section 351 of the PHS Act. In order to clarify the use of these terms, and to facilitate a clearer understanding of the proposed revision of § 601.12, FDA is proposing to amend § 600.3 (21 CFR 600.3) to include definitions of ''supplement'' and ''amendment.'' Previously, a change submitted to an approved biological product license application (PLA) or establishment license application (ELA) was termed an ''amendment.'' In order to achieve consistency with CDER in implementing the Prescription Drug User Fee Act of 1992 (PDUFA)(21 U.S.C. 301, *et seq.*), CBER began using the term ''amendment'' to refer to a change submitted to a pending license application or supplement, and the term ''supplement'' to refer to a change submitted to an approved license application. A change to an unapproved (pending) new drug application (NDA) is also referred to as an ''amendment'' and a change submitted to an approved NDA is also referred to as a ''supplement.'' Under this proposed rule, § 600.3(ff) would define the term ''amendment'' as the submission of information to an unapproved license application or supplement. Such information could include additional information or reanalysis of data previously submitted, to revise or modify the application as originally submitted. Section § 600.3(gg) would define a ''supplement'' as a request to the Director, CBER, to approve a change to an approved license application. A supplement would ordinarily contain a description of the proposed change and the data and information supporting the change.

FDA believes that defining these terms in the regulations will simplify the approval process for applicants, minimize misunderstanding between CBER and the biologics industry, and harmonize the use of the terms within CBER and CDER.

2. Section 314.70—Changes to an Approved Application

To ensure consistent treatment of well-characterized biotechnology-derived products within CBER and CDER, conforming amendments to § 314.70 are also being proposed. Specifically, FDA is proposing an exception in § 314.70(g) for well-characterized biotechnology products that provides that manufacturing changes to these products would be handled as described in proposed § 601.12(b), (c), and (d) with regard to preapproval, notification, and submission in annual reports instead of as described in § 314.70 (a), (b), (c), and (d). However, labeling changes would not be affected by the proposed change.

3. Summary of Proposed § 601.12—Changes to an Approved Application

Section 601.12 currently requires that important proposed changes in location, equipment, management and responsible personnel, or in manufacturing methods and labeling, be reported to the Director, CBER, not less than 30 days in advance of the time such changes are intended to be made. Proposed changes in manufacturing methods and labeling may not become effective until notification of acceptance is received from the Director, CBER.

In comments made to the public docket and at the January 26, 1995, public meeting, representatives from the biologics industry requested that FDA modify § 601.12 to be more flexible and less burdensome. The representatives also asked that a category system of changes to be reported be implemented, which would include changes that could be made without prior approval and those that would be required to be described in an annual report. Several comments requested that CBER make the reporting process comparable to § 314.70 *Supplements and other changes to an approved application* which sets out three categories of notification of changes that are reported to FDA. These include: Supplements requiring FDA approval before the change is made, supplements for changes that may be made before FDA approval (changes being effected), and changes described in an annual report. Another comment stated that regulations should not stand as a barrier to manufacturing process improvement by requiring the filing of a supplement and CBER approval for even minor changes and improvements in the manufacturing process.

The regulatory scheme that the agency is now proposing responds to these and other requests from the public. In response to the comments, FDA undertook an informal review of the types of changes that had historically been subject to prior approval and the impact such changes had on products and establishments. FDA also examined the existing requirements applicable to drugs and devices approved under the act; in particular, the regulations found in §§ 314.70 and 814.39 (21 CFR

814.39). FDA used this information to develop categories of reportable changes and criteria for assigning a change to the appropriate category.

FDA is now proposing a three-category scheme for changes in the product, production process, equipment, facilities, or responsible personnel that would eliminate FDA approval of certain reportable changes and create a category of changes that would be described in an annual report. In addition to these two categories, there is a category of changes which would require approval prior to distribution. The agency believes that this proposed rule reduces unnecessary reporting and approval of changes for biologics licensed under the PHS Act consistent with the corresponding regulations applicable to drugs and devices approved under the act. These categories would include: (1) Supplement submission and approval prior to distribution of a product made using a proposed change that has a substantial potential to have an adverse effect on a product's safety, purity, potency, or effectiveness; (2) notification not less than 30 days prior to distributing a product made using a change that has a moderate potential to have an adverse effect on a product's safety, purity, potency, or effectiveness; and (3) an annual report describing changes that have minimal potential to have an adverse effect on a product's safety, purity, potency, or effectiveness. The agency does not intend that this rule would apply to normal maintenance and repair which would continue to be documented as it is now by firms under applicable current good manufacturing practice (CGMP) regulations (21 CFR parts 210, 211, 606, and 820). The proposed revision also includes new § 314.70(g) for well-characterized biotechnology products to make the requirements for changes made to such products consistent within CBER and CDER.

The proposed revision also sets out a separate, three-category reporting system for biological product labeling changes. This scheme differs slightly from the scheme for proposed changes in the product, production process, equipment, facilities, or responsible personnel, and is consistent with requirements for labeling changes applicable to drugs approved under the act. A change to a product package label, container label, or package insert would require one of the following: (1) Submission of a supplement with FDA approval required prior to product distribution; (2) submission of a supplement with product distribution allowed prior to FDA approval; or (3) submission of the final printed label in an annual report. Promotional labeling and advertising would be required to be submitted in accordance with the requirements of § 314.81(b)(3)(i)(21 CFR 314.81((b)(3)(i)).

Although the proposed decrease in reporting and approval requirements and the corresponding reduction in the agency's role in reviewing changes before they are implemented does present some risks to product safety, purity, potency, and effectiveness, the agency believes that these risks are minimal. Under the proposed rule the applicant would be required to document that each change has no adverse effect on the safety, purity, potency, or effectiveness of the product. Such documentation would include appropriate validation and/or other studies. In some cases clinical data would be necessary and in other cases it would not. Applicants would be required to maintain records of the validation and study data under existing CGMP requirements. For those changes no longer requiring supplement approval, FDA review would shift to postmarketing review including inspections of manufacturing facilities.

The proposed rule includes some specific examples of changes that fall into a particular category, but does not attempt to set out a comprehensive list of the changes included in each category. The agency recognizes that scientific and technological advances may change the need for supplement approval and/or reporting of many types of changes. Moreover, the potential for a particular change to adversely affect a product's safety, purity, potency, or effectiveness may differ for different products. FDA recognizes that a change made to a less well-characterized product could fall into a different reporting category than the same change made to a product that was adequately characterized using analytical and functional tests. For example, scale up of a purification process may have a greater impact on a live virus vaccine than it may on a well-characterized recombinant DNA-derived purified protein. The agency believes that it can more readily respond to advances in technology, differences among products, and knowledge gained from experience by creating a rule that sets out general categories of changes. FDA recognizes, however, that applicants need clear guidance on how the agency intends to interpret the rule in order to efficiently produce products and adhere to regulatory requirements. Accordingly, FDA intends to make available guidance documents to describe the agency's current interpretation of specific changes falling into each category and to modify the documents as needed to reflect changes in science and technology. Notices of availability for drafts of guidance documents for reporting changes to most biological products and to well-characterized recombinant DNA-derived and monoclonal antibody biotechnology products are published elsewhere in this issue of the Federal Register. FDA is seeking comment on the use of guidance documents in conjunction with a final rule that may result from this proposal. FDA is also soliciting comment on the appropriate categorization of specific changes enumerated in this proposal and the guidance documents. In the Federal Register of October 25, 1995, (60 FR 54695), FDA announced that a workshop would be held on December 11 through 13, 1995, to discuss the definition of a well-characterized biotechnology product. Information from this workshop will help FDA to refine its definition of a well-characterized biotechnology product.

FDA also anticipates that applicants could consult with the office which has product or establishment responsibility in CBER, or the Office of New Drug Chemistry in CDER, regarding appropriate objectives and design of studies to validate and document the potential for adverse effect of a proposed change for a particular product prior to committing the resources for such studies. Guidance on the appropriate reporting mechanism would also be available from these offices.

The proposed rule would authorize the Directors of CBER and CDER, or their designees under 21 CFR part 5, to make decisions under the provisions of the rule as they apply to their respective centers.

The agency expects that applicants would update their marketing applications in an annual report to assure that they accurately reflect current conditions. FDA is seeking comments on mechanisms that industry and the public believe may be appropriate for the periodic update of marketing applications. This proposed rule would require that some changes in manufacturing be submitted annually. CBER does not currently require, nor would this proposed rule require, that the annual report include additional information that is submitted for a drug approved under the act under § 314.81(b)(2). FDA requests comment on whether the annual report for a biological product licensed under the

PHS act should include the information described in § 314.81(b)(2).

The proposed rule does not address requirements for submitting changes to a pending license application or supplement. Applicants currently submit amendments to pending applications in order to comply with the requirement in the PHS Act that a biologic product distributed for sale, barter, or exchange in interstate commerce must be manufactured in accordance with its license, and the regulations in § 601.2 that set out the information and data that must be submitted in such license applications. FDA intends to consider whether specific requirements for submitting amendments to pending applications should be included when the agency undertakes a review of the licensing requirements in part 601 (21 CFR part 601).

4. Analysis of § 601.12—Changes to An Approved Application

a. *Changes requiring supplement submission and approval prior to distribution of product made using the change*. Currently, all important proposed changes made by applicants must be reported not less than 30 days in advance of the time such changes are intended to be made. Such changes in manufacturing methods and labeling may not become effective until notification of acceptance is received from the Director, CBER. Accordingly, CBER requires approval of all important changes in manufacturing methods and labeling before such changes are implemented. FDA continues to believe that it is important that the agency review data regarding any change that has a substantial potential to have an adverse effect on the safety, purity, potency, or effectiveness of the product, prior to distribution of the product made using the change, to assess whether the change will have a detrimental impact on the licensed product with regard to its safety, purity, potency, effectiveness, and consistency in biological and clinical characteristics.

Proposed § 601.12(b)(1) would require an applicant to submit a supplement for approval to the Director, CBER, for any proposed change in the product, production process, equipment, or facilities that has a substantial potential to have an adverse effect on the product's safety, purity, potency, or effectiveness. These changes have the highest probability to adversely affect the product's safety, purity, potency, or effectiveness, and, in most instances, are integral to the manufacturing process or product production equipment. Proposed § 601.12(b)(1) would require the applicant to submit a supplement containing a detailed description of the proposed change, the products involved, the manufacturing sites or areas affected, a description of the methods used and studies performed to evaluate the effect of the change on the product's safety, purity, potency, and effectiveness, the data derived from clinical and/or nonclinical laboratory studies, relevant validation protocols and data, and a reference list of the relevant standard operating procedures (SOP's). Approval of the supplement by the Director, CBER, would be required prior to distributing product made using the change.

FDA proposes to enumerate the following changes that have a substantial potential to have an adverse effect on a product's safety, purity, potency, or effectiveness: A new indication, route of administration, dosing schedule, dosage form, or formulation; the addition, removal, or reordering of the step(s) of the licensed production process; and the conversion of a single product manufacturing area to a multiproduct manufacturing area. The agency believes that the need for FDA premarket approval of these significant changes is unlikely to vary with technological advances or due to differences among products, and that these changes should be enumerated in the rule.

Other examples of changes that have caused detrimental effects on the safety, purity, potency, or effectiveness of products, even where applicants performed validation or other studies, include process changes or changes in analytical methods that result in a change of specification limits and addition of a new location for manufacture. FDA believes that the agency's continued prior review and approval of such changes is currently necessary to protect the public from products whose safety, purity, potency, or effectiveness may be compromised. However, FDA is proposing to describe these, and additional, specific examples of changes that CBER currently believes have substantial potential to adversely affect the product, in guidance, rather than enumerate them in the rule. FDA anticipates that scientific advances and future experience may reduce the need for premarket approval of certain changes and believes that the agency will be able to respond readily to changed circumstances by revising guidance that interprets the rule.

b. *Changes requiring notification not less than 30 days prior to distributing product made using the change*. FDA believes that the public health can be adequately protected by eliminating agency approval of changes that have only a moderate potential to have an adverse effect on the safety, purity, potency, or effectiveness of a product. Changes that have moderate potential to affect a product's safety, purity, potency, or effectiveness are changes that do not have as high a probability for causing an adverse effect as those for which the agency proposes to require supplement approval. Under current § 601.12, the agency requires FDA approval of all important proposed changes to a product, and requires that all important proposed changes in manufacturing methods and labeling await such approval before they may be distributed. FDA is now proposing to require that applicants notify the agency not less than 30 days prior to distributing a product made with a change in the product, production process, equipment, facilities, or responsible personnel that has moderate potential to have an adverse effect on the product, but to permit a product to be distributed after the 30-day period has elapsed without awaiting FDA approval. These notifications would not be considered supplements requiring approval. Thus, many changes that now require FDA approval as supplements could be implemented rapidly through the notification process without the prior submission of a supplement. For example, based on FDA's experience in reviewing submissions, the agency currently believes that minor changes in fermentation batch size using the same equipment and resulting in no change in specifications of the bulk or final product, and increases or decreases in the purification scale, not associated with a process change or different equipment, have moderate potential to have an adverse effect on the product.

In the notification, an applicant would be required to provide the agency with a clear description of the change, the product or products involved, the manufacturing sites or areas involved, a brief description of the validation and/or other clinical and/or nonclinical laboratory studies conducted to analyze the effect of the change on the safety, purity, potency, and effectiveness of the product, the dates of any such studies, reference to any SOP's used to complete the studies, and a summary of the relevant data or information. During the 30-day period, FDA would review the notification to determine if it was properly submitted as a notification. If FDA agreed that the change described was of the type that had moderate potential to adversely affect the safety, purity, potency, or effectiveness of the product, and the notification included

all of the required information, the applicant could begin distribution of a product made using the change 30 days after FDA's receipt of the notification.

Under the proposed rule, FDA would ordinarily contact the applicant before the expiration of the 30-day period if the agency determined that the change was improperly submitted as a notification. If FDA informed the applicant within the 30-day period that the submission did not meet the requirements for a notification, the applicant would be required to correct the deficiencies in the information submitted before distributing the product. Depending on the problem, FDA would respond in one of two ways: (1) If the change was of the type that presented a substantial potential to adversely affect the safety, purity, potency, or effectiveness of the product, the agency would inform the applicant that the change should be submitted as a supplement and the applicant would be required to await FDA approval before product produced with the change could be distributed; or (2) if the change was of the type that could properly be submitted as a notification, but the required information was incomplete, the applicant would be required to supply the missing information and wait until FDA determined compliance with this section before distributing the product.

FDA intends, during the 30 days, to focus its review on determining whether the applicant reported the change under the appropriate mechanism, and, if so, whether any of the required information was missing. Under the proposed rule, FDA would not ordinarily contact the applicant if the notification was properly submitted in accordance with §§ 601.12(c) or 314.70(g)(2). FDA anticipates that applicants would use a method of delivery for notifications that would allow confirmation of the submission having been received by FDA.

FDA would also ordinarily review the substantive information contained in a notification and request the applicant to clarify the submission if necessary. If the agency's review determined that additional studies or information were necessary to document the lack of an adverse effect on the safety, purity, potency, or effectiveness of the product, the agency could request that additional data be collected. Failure to comply with the proposed requirements and existing CGMP requirements to properly validate the change could result in enforcement action. Following the agency's review, FDA would send to the applicant a stamped copy of the cover letter for the notification indicating that FDA had placed the submission in the applicant's license application file. FDA anticipates that the agency could conduct a more extensive review of data supporting the notification during inspections if necessary.

FDA believes that a notification process, as described above, for changes that have a moderate potential to affect the safety, purity, potency, or effectiveness of the product would protect against the distribution of unsafe or ineffective products while speeding the availability of improved products. Under the proposed rule, applicants would be required to demonstrate, through appropriate validation or other studies, that a change has no adverse effect on the safety, purity, potency, and effectiveness of the product. Applicants would be required to briefly describe the studies and data in the notification. While a full description of the studies would not be required to be submitted in a notification, as it generally would be in a supplement, applicants would be required to maintain the data in records that are available for FDA inspection under existing CGMP's. The 30-day period that would be required to elapse before products made using the change could be distributed would permit the agency to redirect submissions for changes that could substantially affect product safety, purity, potency, or effectiveness to the supplement approval process before the product entered the market. In addition, the agency could identify applicants that, through an incomplete submission, failed to establish that they had followed the necessary steps to validate and implement a change. Applicants would be required to submit the missing information before they could distribute the product.

c. *Changes to be described in an annual report.* FDA recognizes that there are changes in the product, production processes, equipment, facilities, and responsible personnel that have minimal potential to have an adverse effect on the product's safety, purity, potency, or effectiveness. Under the current § 601.12, the agency has required many of these changes to await supplement approval before they could be implemented. FDA believes that prior agency approval of these changes is unnecessary, and is proposing in § 601.12(d) that such changes would not be required to be approved by the agency. FDA continues to believe that it is important that such changes be documented and validated so that there is a mechanism for assessing the consequences of the change. FDA is therefore proposing that changes that have minimal potential to have an adverse effect on the product's safety, purity, potency, or effectiveness be required to be described by the applicant in an annual report. The annual report would be required to be submitted each year within 60 days of the anniversary date of approval of the application. FDA believes that the agency can effectively assess compliance with this section and CGMP requirements for changes that have minimal potential to adversely affect the product's safety, purity, potency, or effectiveness by having ready access to information regarding such changes through the submission of an annual report and by inspection. Applicants would be required to include in the annual report a listing of all products involved, a brief description of and reason(s) for the change, the manufacturing sites or areas involved, the date each change was made, and a cross-reference to any validation protocols and/or SOP's. Both the applicant and FDA could use this information to assess whether problems which may arise with products are related to such changes. Under proposed § 601.12(a), the applicant would be required to perform appropriate validation or other studies to demonstrate the lack of adverse effect on the safety, purity, potency, and effectiveness of the product. Applicants would maintain records of such studies under existing CGMP requirements.

As a result of FDA's experience in reviewing changes, the agency believes that changes that have a minimal potential to have an adverse effect on the product would include such changes as a change in storage conditions of in-process intermediates based on data derived from studies following a protocol in the approved license application; modifications in analytical procedures with no change in the basic test methodology or existing release specifications; relocation of analytical testing laboratories within a licensed facility; and area upgrades such as the installation of improved finishes on floors or walls.

d. *Labeling.* Under the current § 601.12, all important proposed labeling changes are required to be submitted for FDA approval before they may be implemented. The agency recognizes, however, that some labeling changes may not have a substantial impact on the safe and effective use of the product. For other changes, such as updates of important safety information, it is important that prescribers and patients have access to current information as soon as it becomes available. Therefore, the agency is proposing to revise the biological products reporting requirements for

labeling changes. The regulations in § 314.70(b), (c), and (d), governing how labeling changes are reported for products regulated by CDER, are not affected by the proposal. In fact, the proposed revision of § 601.12(e) is consistent with requirements for labeling changes applicable to drugs approved under the act.

Changes to labeling would be submitted to CBER 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 product with the accompanying revised labeling prior to such approval, or (3) submission of final printed labeling in an annual report. It is expected that proposed § 601.12(e) would significantly decrease the number of labeling submissions that currently require approval prior to use of the labeling.

Under proposed § 601.12(e)(2), an applicant would be required to submit a supplement, but could disseminate the revised labeling with the product, at the time the supplement was submitted. Such revisions to the labeling would include any information that adds or strengthens a contraindication, warning, precaution, or adverse reaction; adds or strengthens a statement about abuse, dependence, psychological effect, or overdosage; adds or strengthens an instruction about dosage and administration that is intended to increase the safe use of the product; or deletes false, misleading, or unsupported indications for use or claims for effectiveness.

FDA believes that permitting these labeling changes to be effected and product distributed prior to FDA approval would facilitate labeling changes intended to adequately inform prescribers and patients of the risks and benefits of a biological product and thereby allow prescribers and patients earlier access to important new information on the safe use of the product. Proposed § 601.12(e)(2) would require that the supplement clearly identify any changes being made and include necessary supporting data. Under the proposed rule, the changes identified in § 601.12(e)(2) could be implemented prior to agency approval. FDA could, however, deny approval of a supplement for a labeling change that has already been disseminated with the product. In assessing an applicant's plans to correct a problem, FDA would consider the applicant's reasons for making the change and the alternatives available to the applicant. If the circumstances warranted, FDA could require the labeling change to be immediately discontinued. However, when circumstances permit, the agency would allow the applicant to correct a problem with minimal expense and without unnecessary waste.

Under proposed § 601.12(e)(3), an applicant making editorial or other minor changes, or a change in the information on how the biologic is supplied that does not involve a change in the dosage strength or dosage form, would be required to submit a description of the changes and all final printed labeling incorporating the changes in an annual report to be submitted to the Director, CBER. For all changes in the package insert, package label, and container label that would not fall under § 601.12(e)(2) or (e)(3), an applicant would be required to submit a supplement supporting the proposed change and await FDA approval prior to distribution.

Under proposed § 601.12(e)(4), promotional labeling and advertising would be submitted in accordance with 21 CFR 314.81(b)(3)(i), which requires that an applicant submit specimens of mailing pieces and any other labeling or advertising devised for promotion of the product at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement for a prescription product.

e. *Failure to comply*. FDA is proposing in § 601.12(f) that in the event of repeated failure of the applicant to comply with § 601.12, the Director, CBER, may require that the applicant submit a supplement for any proposed change and obtain CBER approval prior to distributing the product made using the change. This measure would be in addition to other remedies available in applicable laws and regulations, including suspension or revocation of licenses, seizure of products, and injunction, among others. With this proposed rule, FDA is undertaking to significantly reduce the number of changes that are reported, reviewed, and approved by the agency. Continued protection of the public from products with compromised safety, purity, potency, or effectiveness will depend on applicants' adherence to the proposed requirements to conduct validation and/or other studies to document the lack of adverse effect on the product and utilization of the appropriate mechanism to inform the agency of such changes. In determining repeated failure to comply with the § 601.12 and whether an applicant would be required to file future submissions as supplements, the agency would consider, among other things, the applicant's compliance history and the significance of the deficiencies.

f. *Administrative review*. Proposed § 601.12(g) provides that an applicant may request a review of FDA employee decisions made pursuant to section § 601.12 in accordance with § 10.75 (21 CFR 10.75). Section 10.75 provides a mechanism for internal agency review of decisions. FDA proposes to include the reference to § 10.75 in § 601.12(g) so that applicants who wish agency review of a decision made under the provisions of the rule are made aware of the mechanism for such review. The internal agency review of a decision would be based on the information in the administrative file. FDA believes that it is important for the agency to apply regulations affecting regulated products consistently and fairly, and believes that agency review should be available to resolve a disputed issue.

II. Analysis of Impacts

A. Method of Analysis

To determine the impact of the proposed rule, CBER undertook an analysis of changes approved as supplements during the 9-month period between October 1, 1994, and June 1, 1995. CBER has determined that the proposed rule as currently written would result in an overall 32 percent reduction in submissions requiring prior agency approval before an applicant could commence distributing product made using the change. The extent of the reduction would be greater for certain products. Under the proposed regulation, 88 of 175 submissions reviewed as supplements under the current regulation (for changes to biological products other than blood products and blood component products) would be supplements requiring prior approval, 62 would be notifications to CBER not requiring FDA approval, and 25 would be described in an annual report. For blood and blood components, of 177 supplements approved in a 2-month portion of the 9-month period, 128 would be supplements requiring prior approval under the proposed rule, 36 would be notifications, and 13 would be described in an annual report.

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

FDA has examined the impact of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (Pub. L. 96–354). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select the regulatory

approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this proposed rule is consistent with the regulatory philosophy and principles identified in the Executive Order. The proposed 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 proposed rule would be a substantial reduction in reporting burden for applicants and in review burden for the agency. In addition, FDA anticipates that the proposed rule would encourage applicants to improve their licensed products and methods of manufacture.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because, as stated above, the overall result of the proposed rule would be a substantial reduction of the regulatory and reporting burden, the agency certifies that the proposed 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.

C. Review under the Paperwork Reduction Act of 1995

This proposed rule contains information collections which are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995. The title, description, and respondent description of the information collection 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.

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

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

Description: This proposed rule would change the requirements for respondents to report to FDA changes in the product, labeling, production process, equipment, facilities, or responsible personnel established in an approved application for a biological product or for a well-characterized biotechnology product. The respondent would report the change to FDA in one of the three following ways depending on the potential for the change to have an adverse effect on the safety, purity, potency or effectiveness of the product: (1) Changes that have a significant potential to have an adverse effect on the product would be submitted in a supplement requiring prior approval by FDA before distribution of a product made using the change; (2) changes that have a moderate potential to have an adverse effect on the product would be submitted to FDA in a notification not less than thirty days prior to distribution of the product made using the change; and (3) Changes that have a minimal potential to have an adverse effect on the product would be submitted by the respondent in an annual report.

Labeling changes for a biological product would 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 product with the accompanying revised labeling prior to such approval; or (3) submission of final printed labeling in an annual report. Promotional labeling and advertising would be submitted in accordance with 314.81(b)(3)(i). Labeling changes for well-characterized biotechnology products would not be affected by this proposed rule.

Description of Respondents: All manufacturers and applicants holding a biological license approved under section 351 of the Public Health Services Act and all manufacturers and applicants of well-characterized biotechnology products holding an approved NDA would report (Business or other for-profit).

These estimates are an approximation of the average time expected to be necessary for a collection of information. They are based on such information as is available to FDA. There are no capital costs associated with this information collection. It is estimated that 20 percent of all reports required under these proposed regulations are being prepared by contractors. The burden hours in the chart below therefore reflect a 20 percent reduction per regulation because these burden hours will not be expended by the affected industry rather they will be expended by the contractors. 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 column labeled ''Operating and Maintenance Costs.''

The agency seeks comments on these estimates, particularly the industry's view of the number of firms and products affected by the collections of information contained in this proposed rule.

Estimated Annual Burden

Regulation (21 CFR)	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	610	1.56	$390,400	39,040
601.12(c)	391	40	280	0.72	$89,600	8,960
601.12(d)	391	10	110	0.28	$8,800	880
601.12(e)(1)	391	40	200	0.51	$64,000	6,400
601.12(e)(2)	391	20	20	0.05	$3,200	320
601.12(e)(3)	391	10	220	0.56	$17,600	1,760
601.12(e)(4)	391	10	110	0.28	$8,000	800

Estimated Annual Burden						
Regulation (21 CFR)	Number of Respondents	Hours Per Response	Number of Responses	Number of Responses Per Respondent	Total Operating and Maintenance Costs	Total Hours Per Regulation
314.70(g)(1)	4	80	50	12.5	$32,000	3,200
314.70(g)(2)	2	40	3	1.5	$960	96
314.70(g)(3)	6	10	20	3.33	$1,600	160
Totals					Total O&M Costs = $616,160	Total Hours = 61,616

The agency has submitted a copy of this proposed rule to OMB for its review and approval of these information collections. Interested persons are requested to send comments regarding this information collection, including suggestions for reducing this burden to the Office of Information and Regulatory Affairs, OMB, New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington, DC 20503, Attn: Desk Officer for FDA. Submit written comments on the information collection by February 28, 1996, but not later than March 29, 1996.

D. Review Under the National Environmental Policy Act

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.

Interested persons may, on or before April 29, 1996, submit to the Dockets Management Branch (address above) written comments regarding the proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. Submit comments on the information collection requirements to the Office of Information and Regulatory Affairs, OMB, (address above).

As stated previously, FDA plans to hold an open public meeting during the comment period to facilitate public comment on this proposed rule. The time and location of this meeting will be announced in a future issue of the Federal Register.

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.

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, it is proposed that 21 CFR parts 314, 600, and 601 be 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 new paragraph (g) as follows:

§ 314.70 Supplements and other changes to an approved application.

* * * * *

(g) *Exception.* An applicant proposing to make a change in a well-characterized biotechnology product of the type described in § 314.70(a), (b)(1), (b)(2), (c)(1), (c)(3), (d)(1), and (d)(4) through (d)(9) shall comply with the following:

(1) *Changes requiring supplement submission and approval prior to distribution of product made using the change.* (i) A supplement shall be submitted for any proposed change in the product, production process, equipment, or facilities that has substantial potential to have an adverse effect on the safety, purity, potency, or effectiveness of the product. These changes include but are not limited to:

(A) A new indication, route of administration, dosage form, dosing schedule or formulation;

(B) Addition, removal, or reordering of the step(s) of the production process; and

(C) Change from production of a single product to production of multiple products at a facility.

(ii) The applicant shall obtain FDA approval of the supplement prior to distribution of the product made using the change. The following information 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 product's safety, purity, potency, and effectiveness;

(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 notification not less than 30 days prior to distributing product made using the change.* (i) An applicant shall inform FDA, in a written notification labeled ''Notification—Changes being effected in 30 days,'' of any change in the product, production process, equipment, facilities, or responsible personnel that has moderate potential to have an adverse effect on the safety, purity, potency, or effectiveness of the product. Distribution of the product manufactured after the change was instituted may not begin until 30 days after FDA notification. The following information shall be contained in the notification:

(A) A clear, brief description of the change;

(B) The products(s) involved;

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

(D) A brief description of the validation and/or other studies

conducted to analyze the effect of the change on the safety, purity, potency, and effectiveness of the product;

(E) The dates of the studies;

(F) Reference to relevant SOP's used to complete the studies; and

(G) A summary of the relevant data or information.

(ii) If within 30 days following FDA's receipt of the notification FDA informs the applicant that either:

(A) The change requires supplement submission in accordance with paragraph (g)(1) of this section; or

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

(3) *Changes to be described in an annual report.* Changes in the product, production process, equipment, facilities, or responsible personnel that have minimal potential to have an adverse effect on the product's safety, purity, potency, or effectiveness, 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 annual report shall contain the following information for each change:

(i) A list of all products involved;

(ii) A brief description of and reason(s) for the change;

(iii) The manufacturing sites or areas involved;

(iv) The date each change was made; and

(v) A cross-reference to relevant validation protocol(s) and/or SOP's.

* * * * *

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 in this section, an applicant shall inform the Director, Center for Biologics Evaluation and Research (CBER), about each change in the product, labeling, production process, equipment, facilities, or responsible personnel 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 nonclinical laboratory studies the lack of adverse effect of the change on the safety, purity, potency, and effectiveness of the product. Single copies of Food and Drug Administration (FDA) guidance describing FDA's current interpretation of this regulation may be obtained from the Congressional and Consumer Affairs Branch (HFM–12), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448.

(b) Changes requiring supplement submission and approval prior to distribution of product made using the change.

(1) A supplement shall be submitted to the Director, CBER, for any proposed change in the product, production process, equipment, or facilities that has substantial potential to have an adverse effect on the safety, purity, potency, or effectiveness of the product. These changes include but are not limited to the following:

(i) A new indication, route of administration, dosage form, dosing schedule or formulation;

(ii) Addition, removal, or reordering of the step(s) of the licensed production process; and

(iii) Change from production of a single product to production of multiple products at a licensed facility;

(2) The applicant shall obtain approval of the supplement from the Director, CBER, prior to distribution of the product made using the change. The following information 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 product's safety, purity, potency, and effectiveness;

(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 notification not less than 30 days prior to distributing product made using the change.* (1) An applicant shall inform the Director, CBER, in a written notification labeled ''Changes being effected in 30 days,'' of any change in the product, production process, equipment, facilities, or responsible personnel that has moderate potential to have an adverse effect on the safety, purity, potency, or effectiveness of the product. Distribution of the product manufactured after the change was instituted may not begin until 30 days after receipt of the notification by CBER. The following information shall be contained in the notification:

(i) A clear, brief description of the change;

(ii) The product(s) involved;

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

(iv) A brief description of the validation and/or other studies conducted to analyze the effect of the change on the safety, purity, potency, or effectiveness of the product;

(v) The dates of the studies;

(vi) Reference to relevant SOP's used to complete the studies; and

(vii) A summary of the relevant data or information.

(2) If within 30 days following FDA receipt of the notification, the Director, CBER informs the applicant that either:

(i) The change requires supplement submission in accordance with paragraph (b) of this section; or

(ii) Any of the information required under paragraph (c)(1) of this section is missing, the applicant shall not distribute the product made with the change until compliance with this section is achieved.

(d) *Changes to be described in an annual report.* (1) Changes in the product, production process, equipment, facilities, or responsible personnel that have minimal potential

to have an adverse effect on the product's safety, purity, potency, or effectiveness, 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 annual report shall contain the following information for each change:

(i) A list of all products involved;

(ii) A brief description of and reason(s) for the change;

(iii) The manufacturing sites or areas involved;

(iv) The date each change was made; and

(v) A cross-reference to relevant validation protocol(s) and/or SOP's.

(2) 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 section obtained for each change made during the annual reporting interval which ends on the anniversary date.

(e) *Labeling changes*—(1) *Label changes requiring supplement submission—distribution of a product with a label change must await FDA approval.* An applicant shall submit to CBER a supplement describing a proposed change in the package insert, package label, or container label, except those described in paragraphs (e)(2) and (e)(3) of this section, and include the information necessary to support the proposed change. The supplement shall clearly highlight the proposed change in the label. The applicant shall obtain approval from the Director, CBER, prior to distributing a product with the label change.

(2) *Label changes requiring supplement submission; product with a label change may be distributed before FDA approval.* (i) An applicant shall submit to CBER, 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, overdosage;

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

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

(ii) 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 should be plainly marked: ''Special Labeling Supplement—Changes Being Effected.''

(3) *Label 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 to CBER in an annual report submitted each year within 60 days of the anniversary date of approval of the application:

(A) Editorial or similar minor changes; or

(B) A change in the information on how the drug 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 in accordance with the requirements set forth in § 314.81(b)(3)(i) of this chapter, except that Form FDA–2567 shall be used in lieu of Form FDA–2253.

(f) *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, the Director, CBER, may require that the applicant submit a supplement for any proposed change to, and obtain approval of the supplement from, the Director, CBER, prior to distributing a product made using the change.

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

Dated: January 16, 1996.

William B. Schultz,

Deputy Commissioner for Policy.

[FR Doc. 96–1580 Filed 1–25–96; 10:41 am]

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21 CFR Parts 600 and 601

[Docket No. 95D–0415]

Draft Guidance; Changes To An Approved Application for Well-Characterized Therapeutic Recombinant DNA-Derived and Monoclonal Antibody Biotechnology Products; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule; notice of availability.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a draft guidance document entitled ''Draft Guidance; Changes to An Approved Application for Well-Characterized Therapeutic Recombinant DNA-Derived and Monoclonal Antibody Biotechnology Products.'' This draft guidance is intended to assist applicants in determining how they should report changes to an approved license application for well-characterized therapeutic recombinant DNA-derived and monoclonal antibody biotechnology products under the proposed revision to the biologics regulations issued elsewhere in this issue of the Federal Register. In a separate document also published in this issue of the Federal Register, FDA is announcing the availability of a guidance document to assist applicants in determining how they should report changes to an approved license application for biologic products other than well-characterized therapeutic recombinant DNA-derived and monoclonal antibody biotechnology products under the proposed rule. FDA does not intend for these draft guidance documents to be used at this time. The agency is providing these guidance documents for public comment only.

DATES: Written comments by April 29, 1996.

ADDRESSES: Submit written requests for single copies of the draft guidance entitled ''Draft Guidance; Changes to An Approved Application for Well-Characterized Recombinant DNA-Derived and Monoclonal Antibody Biotechnology Products'' to the Congressional and Consumer Affairs Branch (HFM–12), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448, 301–594–1800 or call FDA's automated information system at 800–835–4709. Send two self-addressed adhesive labels to assist that office in processing your requests. Submit written comments on the draft guidance to the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857. Two copies of any comments are to be submitted, except that individuals may submit one copy. Requests and comments should be identified with the docket number found in brackets in the heading of this document. A copy of the draft guidance and received comments are available for public examination in