DEPARTMENT OF ENERGY

Federal Energy Regulatory Commission

18 CFR Part 35

[Docket Nos. RM95–8–000 and RM94–7–001]

Promoting Wholesale Competition Through Open Access Non-Discriminatory Transmission Services by Public Utilities; Recovery of Stranded Costs by Public Utilities and Transmitting Utilities

January 19, 1996.

AGENCY: Federal Energy Regulatory Commission.

ACTION: Proposed rule; extension of time for comments on Draft Environmental Impact Statement (DEIS).

SUMMARY: On November 17, 1995, the staff of the Federal Energy Regulatory Commission issued a draft environmental impact statement for the proposed rule in this proceeding (60 FR 58304, November 27, 1995). On January 3, 1996, an extension of time for the filing of comments on the DEIS was granted because certain departments and agencies of the Federal government were closed for all but emergency matters due to a lack of appropriated funds.

DATES: Comments by all parties shall be filed on or before February 2, 1996.

ADDRESSES: Federal Energy Regulatory Commission, 888 First Street, N.E., Washington, D.C. 20426.

FOR FURTHER INFORMATION CONTACT: Bill Meroney, Office of Economic Policy, (202) 208–1069.

Lois D. Cashell,

Secretary.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 600 and 601

[Docket No. 95N–0411]

RIN 0910–AA68

Well-Characterized Biotechnology Products; Elimination of Establishment License Application

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend the biologics regulations to eliminate the establishment license application (ELA) requirement for well-characterized biotechnology products licensed under the Public Health Service Act (PHS Act). The proposed rule would also exempt well-characterized biotechnology products licensed under the PHS Act from certain biologics regulations and harmonize the requirements applicable to these products with those applicable to similar drug products which are approved under the Federal Food, Drug, and Cosmetic Act (the act).

This action is part of FDA's continuing effort to achieve the objectives of the President's ''Reinventing Government'' initiatives, and it is intended to reduce unnecessary burdens for industry without diminishing public health protection.

DATES: Written comments on this proposed rule by February 28, 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 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.

FOR FURTHER INFORMATION CONTACT: Tracey H. Forfa, Center for Biologics Evaluation and Research (HFM–630), Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448, 301–594–3074.

SUPPLEMENTARY INFORMATION

I. Background

In the Federal Register of December 8, 1995 (60 FR 63048), the agency announced its interim definition of a well-characterized therapeutic recombinant DNA-derived and monoclonal antibody biotechnology product, 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.

A well-characterized therapeutic recombinant DNA-derived and monoclonal antibody product requires proper raw material controls, process validation and controls, and sensitive and validated test methods and specifications.

As announced in the Federal Register of October 25, 1995 (60 FR 54695), FDA held a scientific workshop on December 11, 12, and 13, 1995, to discuss the definition of a well-characterized therapeutic recombinant DNA-derived and monoclonal antibody product and to identify the information necessary to characterize such products. FDA intends to consider information received at the workshop, as well as comments received in response to this proposed rule, to determine whether the definition previously given in this document should be expanded to include other categories of products that would be considered to be well-characterized, such as certain vaccines and biologic devices, e.g., test kits for screening blood.

FDA is proposing to use the phrase ''well-characterized biotechnology product,'' to describe the products that would be eligible for a single license application so that the regulatory language would accommodate such additional categories of products. FDA has not included a definition of a well-characterized biotechnology product in the proposed regulations because the agency intends to clarify the definition in a guidance document that can be more readily modified to reflect changes that may be warranted as scientific knowledge progresses. FDA specifically invites public comment on whether a definition of a well-characterized biotechnology product should be included in the regulations and, if so, what the scope of such a definition should be.

Well-characterized therapeutic recombinant DNA-derived and monoclonal antibody products that are viruses, therapeutic sera, toxins, antitoxins, vaccines, blood, blood components or derivatives, allergenic products, or analogous products applicable to the prevention, treatment, or cure of human diseases or injuries are ''biologics'' within the meaning of

section 351 of the PHS Act (42 U.S.C. 262). They are also ''drugs'' as the term is defined in section 201(g) of the act (21 U.S.C. 321(g)). Additional well-characterized biotechnology products identified in the future may be ''devices'' as defined in section 201(h) of the act (21 U.S.C. 321(h)). Therefore, such products are subject to the provisions of the act applicable to drugs and/or devices, including, but not limited to, the adulteration and misbranding provisions (21 U.S.C. 351 and 352).

At the present time, these products are regulated by either FDA's Center for Biologics Evaluation and Research (CBER) or Center for Drug Evaluation and Research (CDER). CBER and CDER have entered into an intercenter agreement announced in the Federal Register of November 21, 1991 (56 FR 58760), with respect to the regulation of drugs and biological products. The intercenter agreement assigns jurisdiction to CBER or CDER based on product class. A product class is defined as a distinct category of agents recognizable by physical characteristics, source materials, or pharmacologic properties. Examples of product classes include: antibiotics, vaccines, hormones, and human blood derivatives. Under the agreement, some well-characterized biotechnology products, such as recombinant insulin and human growth hormone, are assigned to CDER, while other similar recombinant products, such as erythropoietin, colony stimulating factor, and interferon, are assigned to CBER.

Currently, when approved under the PHS Act as biological products, well-characterized biotechnology products are reviewed like any other biologic; that is, both a product license application (PLA) and an ELA are submitted to and approved by FDA before the well-characterized biotechnology product may be shipped. When approved under the act as a drug product, a well-characterized biotechnology product must have an approved new drug application (NDA) in place of a PLA and ELA. Much of the information provided in a PLA is similar to that included in an NDA. Some of the information provided in an ELA is included in the chemistry, manufacturing and controls section of the NDA (see § 314.50(d)(1)(21 CFR 314.50(d)(1))); however, much of the information concerning the manufacturing facility that is included in an ELA is not included in an NDA.

Technical advances over the last 15 years have greatly increased the ability of manufacturers to control and analyze the manufacture of many biotechnology-derived biological products. After over a decade of experience with these products, the agency has found that it can review the safety, purity, potency, and effectiveness of most well-characterized biotechnology products without requiring submission of a separate ELA. Accordingly, FDA is proposing procedures under which CBER would approve well-characterized biotechnology products by requiring a single biologics license application. CDER would continue to approve NDA's for well-characterized biotechnology products. The single biologics license application and the NDA would have an identical format and include the same information. FDA would continue to inspect manufacturing facilities for compliance with good manufacturing practice requirements before approving either a biologics license application or NDA.

FDA has determined that the review standards for well-characterized biotechnology products across the agency are substantially identical, notwithstanding that such standards may be specified in separate regulations, but the manner in which information is submitted to FDA is more burdensome when done through the ELA mechanism. Accordingly, the agency believes that the proposed procedures will significantly reduce burdens without reducing the safety or effectiveness of these products.

II. Legal Authority

This proposal would establish a licensing scheme for well-characterized biotechnology products that differs from the current licensing scheme in four fundamental ways. First, an applicant seeking marketing approval of a well-characterized biotechnology product would submit a single biologics license application to CBER and be issued a single license. Second, for these products, many of the establishment standards set forth in part 600 (21 CFR part 600) would be exempted from applicability and the current good manufacturing practice requirements found at parts 210 and 211 (21 CFR parts 210 and 211) would constitute the bulk of the applicable establishment standards. Some of the product standards set forth in part 610 (21 CFR part 610) would also be eliminated for these products. Third, in lieu of submitting an ELA to CBER showing compliance with establishment standards, FDA would evaluate whether establishment standards had been met by reviewing information submitted in the biologics license application and by inspecting the facilities in which the product is manufactured. Fourth, the term ''manufacturer'' as it is used in parts 600 through 680 (21 CFR parts 600 through 680) would be broadened to include an applicant for a license for a well-characterized biotechnology product who may or may not own the facilities engaged in significant production steps. This would allow a single license applicant to take responsibility for compliance with the requirements in parts 600 through 680 applicable to manufacturers and eliminate the requirement that each separate contract facility engaging in significant manufacturing obtain a separate license.

These licensing procedures for well-characterized biotechnology-derived biological products are authorized by section 351 of the PHS Act. The proposed rule would establish an administrative approach to enforce the requirements in sections 351(a) and (d) of the PHS Act appropriate for current scientific and technological methods applied in the manufacture of these products.

FDA's current regulations to administer and enforce the statutory requirements embody a dual licensing scheme: Applicants must submit to CBER an ELA and a PLA and obtain agency approval of both applications before they may distribute a biological product. Parts 600 through 680 set out establishment and product standards that applicants must meet before FDA issues an establishment or product license. However, a dual licensing scheme is not compelled by the PHS Act.

Section 351(a) of the PHS Act restricts the interstate sale, barter, and exchange of biologics to products manufactured in establishments that have been licensed. Section 351(a) requires that a biologic product be ''propagated or manufactured and prepared at an establishment holding an unsuspended and unrevoked license.'' Section 351(d) authorizes the agency to prescribe regulations for the issuance, suspension, and revocation of licenses: ''Licenses for the maintenance of establishments for the propagation or manufacture and preparation of [biological] products * * * may be issued only upon a showing that the establishment and the products for which a license is desired meet standards, designed to insure the continued safety, purity, and potency of such products, prescribed in regulations, and licenses for new products may be issued only upon a showing that they meet such standards.'' The sole limitation on the agency's discretion to issue biologic licenses is that licenses may only be

issued upon a showing that both the establishment in which the product is prepared and the product meet regulatory standards designed to insure the continued safety, purity, and potency of such products.

The PHS Act does not prescribe requirements for the format or content of license applications. Nor does it direct that there be two forms of license. The clear import of section 351(a) is that the entity responsible for the product and its manufacture should be licensed.

The agency believes that the single biologics license application scheme that FDA is proposing for well-characterized biotechnology products is authorized by the PHS Act because licenses would continue to be issued only after the agency has made a determination that the product and the establishment(s) in which it is manufactured meet applicable regulatory standards. FDA would make its determination as to whether the product and establishment(s) meet applicable regulatory standards after reviewing the information submitted in the biologics license application and after inspecting the manufacturing facilities.

FDA believes that a license holder need not be the legal owner of each facility in which the product is manufactured as long as he or she is responsible for assuring FDA that the product and establishment standards are met. Accordingly, the proposed rule would permit a single license holder to assume control of the production of a well-characterized biotechnology product regardless of whether he or she owns the manufacturing facilities.

FDA also believes that its administrative approach to enforcing the PHS Act can and should change to respond to changing knowledge and experience in reviewing the safety, purity, and potency of biological products.

III. Summary of Proposed Rule

A. Biologics License Application.

The proposed rule would be applicable to applicants seeking marketing approval of well-characterized biotechnology products that are currently licensed under the provisions of the PHS Act.

In an effort to further harmonize the manner in which well-characterized biotechnology products are regulated, the agency is proposing in new § 601.2(c) to eliminate the requirement for a separate ELA for well-characterized biotechnology products licensed under the PHS Act. This proposed regulation would require that an applicant seeking marketing approval of a well-characterized biotechnology product file a single application on a form prescribed by CBER. The form will include a section that is the same as the chemistry, manufacturing, and controls (CMC) section found in an NDA. (See § 314.50(d)(1)). CBER and CDER have prepared a draft form that has been made available for comment. This draft form may be used in the interim until a final form is available. Both CBER and CDER intend to prepare and use the same guidance documents to aid in the preparation of the chemistry, manufacturing, and controls section of an application for a well-characterized biotechnology product. FDA intends that this guidance will be made available to the public by the time of issuance of any final rule resulting from this proposal.

The CMC section of a license application for a well-characterized biotechnology product, like an NDA for a well-characterized biotechnology product, would include the following elements, at a minimum: A full description and characterization of the well-characterized biotechnology product; the names, addresses, and responsibilities of all manufacturers involved in the manufacture and testing of the product; the method of manufacture, including raw materials, solvents, and reagents; process controls and tests; reference standards; specifications and analytical methods; a description of the container and closure system and its compatibility with the well-characterized biotechnology product drug substance; a description of the storage conditions, stability study protocols, and results; a tabulated list of all components; specifications and methods for the drug product's ingredients; methods of manufacturing and packaging of the well-characterized drug product including a floor plan which designates rooms in the manufacturing facilities and operations in each room; specifications and methods for the drug product; any microbiology and drug product stability data; description of any investigational formulation; environmental assessment and method validation.

This proposal would also expand the definition in § 600.3(t) of ''manufacturer'' to include a license applicant for a well-characterized biotechnology product regardless of whether the applicant is personally engaged in significant manufacturing steps.

These proposed changes would facilitate a company's ability to contract out manufacture of its well-characterized biotechnology products. The proposed rule would eliminate the requirement that each separate contract facility engaging in significant production steps submit an ELA and a PLA. Instead, a well-characterized biotechnology product would be covered by a single biologics license application, which lists all manufacturing locations, regardless of how many separate companies are involved in its manufacture. FDA is seeking comment on whether the definition of ''manufacturer'' in § 600.3(t) should also be expanded to include license applicants for products other than well-characterized biotechnology products.

B. Good Manufacturing Practice Requirements.

The establishment standards for well-characterized biotechnology products would continue to include the CGMP regulations found in parts 210 and 211 (21 CFR parts 210 and 211). FDA would review compliance with good manufacturing practice requirements upon inspection and applicants would be required to demonstrate such compliance in order to obtain approval of a biologics license application.

Should well-characterized devices licensed under the PHS Act be identified and be eligible for the new procedures, applicable CGMP regulations would include parts 606 and 820 (21 CFR parts 606 and 820) (for blood and blood components). FDA requests comments on whether a specific reference to part 820 should be included in the rule.

Under section 501(a)(2)(B) of the act, the methods used in, and the facilities or controls used for the manufacture, processing, packing, or holding of a drug must conform to current good manufacturing practice. Because the bulk drug substance, drug component, and bulk drug product meet the definition of ''drug'' in section 201(g)(1) of the act (21 U.S.C. 321(g)(1)), their manufacture also must conform to good manufacturing practice. The CGMP regulations set forth in parts 210 and 211 are intended to apply to the preparation of a finished dosage form, whether or not in packaged form. (See § § 210.3(b)(4) and 211.1(a).) Although these CGMP regulations are not applied to the manufacture of bulk drug components, there are numerous instances where good manufacturing practice for bulk drug substances and bulk drug product components would parallel the requirements set forth in part 211. (See 43 FR 45076.) Because well-characterized biotechnology products can be susceptible to contamination, adequate control over

bulk manufacturing is important. FDA intends to use the standards of part 211 as guidelines during inspections of manufacturers of bulk drug substance and bulk drug product components, under the jurisdiction of the act, to help ensure that a well-characterized biotechnology product will have the proper raw materials controls, process validation and controls, and sensitive and validated test methods and specifications that are necessary to assure the safety, purity, potency, and effectiveness of the product.

C. Applicability of Current Regulations (Parts 600–680).

In order to harmonize the regulatory standards applied by CBER and CDER in their review of applications for well-characterized biotechnology products, FDA is proposing to exempt well-characterized biotechnology products licensed under the PHS Act from certain requirements found in parts 600 through 680. The regulations that have not been excluded in this proposed rule are those that FDA believes are necessary to ensure the safety, purity, and potency of well-characterized biotechnology products; are essentially the same as those found in comparable regulations governing drug products; may not be applicable by their terms to well-characterized biotechnology products; or are ones that are targeted for revision. FDA requests comments on whether well-characterized biotechnology products should be exempted from requirements in parts 600 through 680 not identified for exclusion in this proposal, or whether certain regulations exempted in this proposed rule should remain applicable. FDA also requests comments on whether well-characterized devices licensed under the PHS Act, should such products be identified, would need to be exempted from the same or different requirements in parts 600 through 680.

The following lists set forth those provisions that FDA proposes would remain applicable, those that FDA proposes to exempt from applicability to well-characterized biotechnology products, and those that would not be applicable by their terms to well-characterized biotechnology products.

The following sections would remain applicable to well-characterized biotechnology products: § § 600.3, 600.10(a), 600.14, 600.20, 600.21, 600.22, 600.80, 600.81, 600.90, 601.2, 601.3(b), 601.4, 601.5, 601.6, 601.7, 601.8, 601.9, 601.12, 601.20, 601.21, 601.22, 601.33, 601.40, 601.41, 601.42, 601.43, 601.44, 601.45, 601.46, 601.50, 601.51, 610.1, 610.2 (Lot-by-lot release eliminated for licensed well-characterized therapeutic recombinant DNA-derived and monoclonal antibody products per letters to manufacturers and notice in the Federal Register of December 8, 1995, (60 FR 63048.)), 610.9, 610.10, 610.11a, 610.12 (Equivalent methods or processes possible under § 610.9.), 610.13, 610.14, 610.15, 610.17, 610.18, 610.30, 610.40, 610.41, 610.45 (Sections 610.40 through 610.45 apply to blood and blood components used in the manufacture of a well-characterized biotechnology product.), 610.50, 610.60, 610.61, 610.63, 610.64, 610.65, and parts 606 (potential applicability to blood and blood components only); 640 (potential applicability to blood and blood products only); and 680 (would apply only to a well-characterized biotechnology allergenic product).

The following sections would be exempted from applicability to well-characterized biotechnology products: §§ 600.10(b) and (c), 600.11, 600.12, 600.13, 601.1, 601.30, 601.31, 601.32, 610.11, 610.53, and 610.62.

The following sections by their terms would not be applicable to well-characterized biotechnology products: §§ 600.15, 601.3(a), 601.10, 601.25, 601.26, 610.16, 610.19, 610.20, 610.21, and parts 607, 620, 630, 650, and 660.

FDA is proposing to exempt well-characterized biotechnology products from the requirements of § 610.11, which sets out procedures for a general safety test for biological products. FDA believes that a general safety test requirement is not necessary to ensure the safety, purity, and potency of a well-characterized biotechnology product. With in-process control and process validation and product testing, the identity of the well-characterized biotechnology product can be determined, its purity can be controlled and quantified, its activity and quantity can be measured, and the end-product release specifications can be validated. The agency believes that specific analytical tests that are available for these products will provide a better assessment of safety than the general safety test.

FDA is also proposing to exempt well-characterized biotechnology products from § 610.62, which sets out requirements for position and prominence of the proper name of the product on the package label. FDA believes that the requirements in § 201.10(g) are adequate to assure the appropriate identification of these products.

D. Transition Issues.

Any well-characterized biotechnology product for which a PLA and an ELA are pending on the effective date of these regulations would be reviewed as submitted. No new submission would be necessary to implement this rule change for these products. If found acceptable for licensure, FDA would issue a biologics license in lieu of issuing both a product and establishment license. Any company planning to file a PLA or an ELA prior to April 1996 should contact the agency for guidance. FDA specifically asks for comments on how transition issues should be handled.

FDA anticipates that applicants already holding an approved ELA and PLA for a well-characterized biotechnology product would not be required to file supplements to comply with the new requirements. The approved PLA for a well-characterized biotechnology product, together with the limited portions of the approved ELA relevant to the new requirements for the biologics license application, would be deemed to constitute an approved biologics license application under the new regulations.

IV. Proposed Effective Date

FDA proposes that a final rule resulting from this proposal become effective upon its date of publication in the Federal Register. As provided under 5 U.S.C. 553(d) and 21 CFR 10.40(c)(4), the effective date of a final rule may not be less than 30 days after publication, except for, among other things, ''a regulation that grants an exemption or relieves a restriction'' (§ 10.40(c)(4)(i)). Because, as described below, this rule would decrease the regulatory burdens for well-characterized biotechnology products, FDA believes that an immediate effective date is appropriate.

V. Analysis of Impacts

A. Reduction in Burden

The proposed harmonization of the requirements would reduce burden on industry because companies manufacturing well-characterized biotechnology products that are regulated by both CBER and CDER would be able to submit applications for products in a consistent format.

Companies developing and manufacturing well-characterized biotechnology products regulated by CBER would no longer have to prepare an ELA to submit to the agency for approval. The amount of information that applicants would need to provide in a biologics license application would be less than that currently required in a PLA and ELA. These proposed changes would enable companies to devote more resources to ensuring that

manufacturing processes are properly validated and fewer resources to submitting documentation to the agency. These changes would especially benefit biotechnology companies that lack experience preparing ELA's and PLA's. According to the biotechnology industry, preparation and submission of an ELA may add substantially to the cost of obtaining approval of a well-characterized biotechnology product.

The inclusion of parts 210 and 211 in the proposed rule as establishment standards would not impose any additional burden on industry. Human drugs, including well-characterized biotechnology products, are already subject to the CGMP's in parts 210 and 211.

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 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 proposed rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, 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 burdens on applicants filing for approval of a well-characterized biotechnology product. In addition, FDA anticipates that the proposed rule would facilitate applicants' ability to improve their licensed products and methods of manufacture by decreasing the burden and cost associated with filing an application.

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 previously, the overall result of the proposed rule would be a substantial reduction of the regulatory and reporting burdens, the agency certifies that the proposed rule would not have a significant negative 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 collection requirements 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 for the 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: Well-characterized Biotechnology Products; Elimination of Establishment License Application.

Description: FDA is proposing to eliminate the requirement that an ELA be submitted and approved by FDA for those well-characterized biotechnology products that are licensed by CBER. For these products, in place of the ELA, a company would be required to prepare and submit additional information for inclusion in a single biologics license application, which would be the same as the information included in the ''Chemistry, manufacturing, and controls'' (CMC) section of a NDA. This proposed regulation would harmonize the approval and other regulatory requirements for all well-characterized biotechnology product under the PHS Act or approved as a drug under the new drug provisions of the act.

Description of Respondents: All applicants for a biological product license to be approved under the Public Health Service Act.

Estimated Annual Reporting Burden

CFR Section	Number of Respondents	Frequency of Responses	Total Annual Responses	Hours per Response	Total Hours
601.2(c)	1	1	1	40	40

Reporting or Disclosure: 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 or operating and maintenance costs associated with this information collection. The number of respondents is dependent in part, on the definition of ''well-characterized biotechnology products,'' now under review by the agency. At the present time, FDA estimates the number of respondents at one a year. The agency seeks comment on these estimates, particularly the industry's view of the number of firms and products affected by the collections of information requirements contained in this proposed rule.

The agency has submitted a copy of this proposed rule to OMB for its review 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. 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.

Interested persons may, on or before February 28, 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. Two copies of all comments are to be submitted, except that individuals may submit one copy. The comments received are available for public examination in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday. Submit written comments on the information collection requirements to the Office of Information and Regulatory Management, OMB (address above).

List of Subjects

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 authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR parts 600 and 601 be amended as follows:

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 revising paragraph (t) to read as follows:

§ 600.3 Definitions.

* * * * *

(t) *Manufacturer* means any legal person or entity engaged in the manufacture of a product subject to license under the act; ''Manufacturer'' also includes an applicant for a license for a well-characterized biotechnology product.

* * * * *

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 601.2 is amended by adding a sentence at the end of paragraph (a) and by adding a new paragraph (c) to read as follows:

§ 601.2 Applications for establishment and product licenses; procedures for filing.

(a) * * * In lieu of the procedures described in this paragraph, applications for well-characterized biotechnology products shall be handled as set forth in paragraph (c) of this section.

* * * * *

(c) *Well-characterized biotechnology products.* (1) To obtain marketing approval for a well-characterized biotechnology product, an applicant shall submit to the Director, Center for Biologics Evaluation and Research, a biologics license application on a form prescribed by the Director, Center for Biologics Evaluation and Research. For such well-characterized biotechnology products, a separate establishment license application shall not be required. An application for a license for a well-characterized biotechnology product shall include: Data derived from nonclinical laboratory and clinical studies that demonstrate that the manufactured product meets prescribed standards of safety, purity, and potency; with respect to each nonclinical laboratory study, either a statement that the study was conducted in compliance with the requirements set forth in part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance; statements regarding each clinical investigation involving human subjects contained in the application, that it either was conducted in compliance with the requirements for institutional review set forth in part 56 of this chapter or was not subject to such requirements in accordance with §§ 56.104 or 56.105 of this chapter, and was conducted in compliance with requirements for informed consent set forth in part 50 of this chapter; a full description of manufacturing methods; data establishing stability of the product through the dating period; sample(s) representative of the product to be sold, bartered, or exchanged or offered, sent, carried or brought for sale, barter, or exchange; summaries of results of tests performed on the lot(s) represented by the submitted samples; and specimens of the labels, enclosures, and containers proposed to be used for the product. An application for license shall not be considered as filed until all pertinent information and data have been received from the applicant by the Center for Biologics Evaluation and Research. The applicant shall also include either a claim for categorical exclusion under § 25.24 of this chapter or an environmental assessment under § 25.31 of this chapter.

(2) Approval of the biologics license application and issuance of the biologics license shall constitute a determination that the establishment and the product meet applicable standards established in this chapter to ensure the continued safety, purity, and potency of such products. Applicable standards for the maintenance of establishments for the manufacture of well-characterized biotechnology product shall include the good manufacturing practice requirements set forth in parts 210 and 211 of this chapter. The following sections in parts 600 through 680 of this chapter shall not be applicable to well-characterized biotechnology products: § § 600.10(b) and (c), 600.11, 600.12, 600.13, 601.1, 601.30, 601.31, 601.32, 610.11, 610.53, and 610.62 of this chapter.

(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,