21 CFR Parts 600 and 601

[Docket No. 95N–0411]

RIN 0910–AA71

Elimination of Establishment License Application for Specified Biotechnology and Specified Synthetic Biological Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the biologics regulations to eliminate the establishment license application (ELA) requirement for certain biotechnology and synthetic biological products subject to licensing under the Public Health Service Act (PHS Act). This final rule also exempts these biotechnology and synthetic biological products from certain biologics regulations and harmonizes 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 final rule 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.

EFFECTIVE DATE: May 24, 1996.

FOR FURTHER INFORMATION CONTACT: Sharon A. Carayiannis, Center for Biologics Evaluation and Research (HFM–630), Food and Drug Administration, 1401 Rockville Pike, suite 400S, Rockville, MD 20852–1448, 301–594–3074.

SUPPLEMENTARY INFORMATION:

I. Background

In the Federal Register of January 29, 1996, FDA proposed to amend the biologics regulations to eliminate the ELA requirement for well-characterized biotechnology products licensed under the PHS Act. In that document, FDA proposed to use the general phrase ''well-characterized biotechnology product,'' to describe products that would be eligible for a single license application so that the regulatory language would accommodate categories of products that might later be considered to be well-characterized as scientific knowledge progresses. FDA requested specific comments 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.

The agency noted that 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 proposed procedures under which CBER would approve most well-characterized biotechnology products by requiring a single biologics license application. FDA noted that the proposed procedures would significantly reduce burdens without reducing the safety or effectiveness of these products.

In the Federal Register of December 8, 1995 (60 FR 63048), the agency first published an interim definition of a well-characterized therapeutic recombinant DNA-derived and monoclonal antibody biotechnology product and announced that, under § 610.2, the Director of CBER was no longer requiring that manufacturers of these products submit samples and protocols to CBER for lot-by-lot release. While the interim definition was intended to be used as a basis for determining which products would be exempted from CBER lot-by-lot release, FDA also used the interim definition to prepare draft guidance on reporting post-approval changes for biotechnology products (as published in the Federal Register of January 29, 1996 (61 FR 2739 at 2748), ''Draft Guidance; Changes to An Approved Application for Well-Characterized Therapeutic Recombinant DNA-Derived and Monoclonal Antibody Biotechnology Products''.)

In addition, FDA held a scientific workshop on December 11 through 13, 1995, to discuss the characterization of therapeutic recombinant DNA-derived and monoclonal antibody products, including whether FDA's interim definition should be changed or expanded to include other categories of products that would be considered well-characterized.

After considering the public comments received on the interim definition, the discussion at the workshop, and the many requests the agency has received for further clarification of the term ''well-characterized,'' FDA has determined that it may not be possible to achieve a sufficiently clear and specific understanding of this term to adequately apprise potential applicants of the applicability of the new procedures. Accordingly, in this final rule, FDA is specifying, in lieu of the term ''well characterized biotechnology product,'' the categories of products to which this final rule will be applicable (see comment Nos. 1 and 6).

FDA intends to evaluate the application of lot-by-lot release for additional products and to announce in the Federal Register a revised determination of which products will be exempted from lot-by-lot release. FDA also plans to issue guidance on the characterization of product categories specified in this rule. FDA anticipates that these documents will replace the notice published in the Federal Register of December 8, 1995 (60 FR 63048).

This final rule is part of FDA's continuing effort to achieve the objectives of the President's ''Reinventing Government'' initiatives. One goal of these initiatives is to harmonize regulations administered by FDA's Center for Biologics Evaluation and Research (CBER) and Center for Drug Evaluation and Research (CDER), to reduce unnecessary burdens for industry without diminishing public health protection.

II. Proposed Rule

In the January 29, 1996, proposed rule, FDA proposed to amend § 601.2(a) and to add a new paragraph (c) to create a licensing scheme for well-characterized biotechnology products that differs from the current licensing scheme for biological products in four fundamental ways. First, an applicant seeking marketing approval for a product that falls within the scope of the rule would submit a single biologics license application to CBER and would be issued a single license. Second, for these products, many of the establishment and product standards set forth in parts 600 through 680 (21 CFR parts 600 through 680) would not be applied. The current good manufacturing practice (CGMP) regulations found at parts 210 and 211 (21 CFR parts 210 and 211), in addition to the information included in a chemistry, manufacturing, and controls (CMC) section of the biologics license application, would constitute the bulk of the applicable establishment standards for these products. Third, in lieu of reviewing an ELA, FDA proposed to 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 for compliance with applicable requirements, including CGMP's. Fourth, FDA proposed to amend § 600.3(t) to broaden the term

''manufacturer'' as it is used in parts 600 through 680 to include an applicant for a license for a well-characterized biotechnology product who may or may not own the facilities engaged in significant manufacturing steps. This amendment would allow a single license applicant to take responsibility for compliance with the requirements in parts 600 through 680 applicable to manufacturers and would eliminate the requirement that each contract facility engaged in significant manufacturing obtain its own license. Instead, each well-characterized biotechnology product could be covered by a single biologics license application, which lists all manufacturing locations, regardless of how many separate companies are involved in its manufacture. In addition, FDA requested comments 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.

III. Responses to Letters of Comment

FDA allowed 30 days for comment on the proposal of January 29, 1996. Written comments received in response to the proposal are on file in the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857.

FDA received seven comments in response to the proposed rule. The comments, which addressed a number of issues, were received from manufacturers of biotechnology products, a blood establishment, and a biotechnology trade association. Comments received and FDA's responses to the comments are discussed below. All of the comments supported the proposal, although many comments contained suggestions or requests for clarification. All of the letters supported FDA's efforts to achieve the President's ''Reinventing Government'' initiatives and agreed that the proposed changes will contribute to the goal of reducing unnecessary burdens for industry and the agency without diminishing public health protection.

1. Two comments requested that FDA define well-characterized products in the final rule to clearly identify those entities subject to the rule and to allow for public comment and administrative review. However, one of these comments also suggested that FDA publish a companion guidance document, updated as necessary, to provide interpretation of this definition based on current technology and scientific knowledge. Two comments requested that a definition be included in a guideline rather than the regulation so that it can be readily revised as the technology advances. One comment stated that the proposal left uncertainty as to which products would be eligible for the single license application.

In response to comments received, FDA has revised its proposed administrative approach and is specifying, in § 601.2(a) and new paragraph (c), the categories of products subject to the rule. FDA has decided to list the product categories in the regulation in order to minimize uncertainty about which products are eligible for the new procedures.

2. Five comments suggested that products in addition to those identified in FDA's interim definition of a well-characterized therapeutic recombinant deoxyribonucleic acid (DNA) derived and monoclonal antibody biotechnology product could be considered well-characterized and requested that FDA broaden the scope of the proposed rule to include additional product categories. Particular categories suggested by one or more comments include: Proteins, including those isolated from natural sources; products (including vaccines and in vitro diagnostics) made using synthetic peptides, recombinant DNA technology and monoclonal antibody technology; products made using chemical synthesis; DNA plasmid products; highly purified and inactivated vaccines; polysaccharides; and any other biologic product for which the applicant submits data from studies that demonstrate that the manufactured product meets prescribed standards of safety, purity, and potency. One comment suggested that in vitro diagnostic products using biotechnology components should not be treated differently than well-characterized biotechnology drugs. One comment requested that FDA specify that blood, blood components (including plasma and stem cells), and plasma derivatives (where the raw material is human based) are products which should not be included.

FDA agrees that the elimination of the ELA requirement should apply to product categories beyond those originally identified in the agency's interim definition of a well-characterized therapeutic recombinant DNA-derived and monoclonal antibody biotechnology product. FDA is expanding the scope of this final rule to include additional products, based on the technology of the manufacturing process and the proposed use of the products. At this time, FDA has determined that it has sufficient experience in reviewing investigational and product applications to eliminate the ELA requirements for the following categories of products: Therapeutic DNA plasmid products; therapeutic synthetic peptide products of 40 or fewer amino acids; monoclonal antibody products for in vivo use; and therapeutic recombinant DNA-derived products. Methodologies are now available to characterize these products in a much more rigorous fashion, allowing the products to be more clearly evaluated by end product testing. FDA believes that eliminating the submission for the facility and establishment information will not adversely affect the public health.

FDA disagrees that vaccines and in vitro diagnostic (IVD) products should be included within the scope of this rule at this time because these products raise additional concerns in assessing safety, purity, and potency. For vaccines, safety is a critical concern due to the intended use in a healthy population. For IVD products, FDA believes that the product and establishment standards necessary to ensure continued safety, purity, and potency may differ from those applicable to products included in this rule.

FDA agrees that blood and blood components, including plasma, plasma derivatives, and stem cells, are products which should not fall within the scope of this rule. FDA believes that license applications for these and other naturally derived products should continue to include establishment information at this time. FDA believes that a license application that includes detailed information on the facilities and controls may be necessary to assess the continued safety, purity, and potency of these products. Because these products involve complex issues, such as a risk of contamination with infectious agents, their review requires special expertise and adequate time in order to assess the adequacy of controls in place at the facility. In addition, end product testing of naturally derived products may not be sufficient to detect contamination with infectious agents. FDA intends to continue to assess the need to expand the scope of the rule to include additional categories of products as science and technology advance and as the agency gains experience in regulating biological products under this new scheme.

3. One comment suggested that the use of a single biologics application be applied to all biologic products. Another comment suggested that IVD products be eligible for the single license application.

As outlined in the President's November, 1995, National Performance Review, ''Reinventing the Regulation of Drugs Made From Biotechnology,'' FDA will use a standardized, single application form for all biological and drug product approvals, regardless of which Center regulates them. FDA will make the harmonized form available for public comment through a subsequent rulemaking and will develop guidance to assist applicants in completing the new application form when it is available.

4. One comment suggested that FDA develop a guideline delineating the responsibilities of center and field inspection personnel to avoid confusion. One comment suggested that FDA application reviewers participate in facility inspections to provide continuity.

FDA recognizes that close cooperation between center and field is essential to the success of this approach. CBER and the field offices intend to coordinate pre- and post-licensure inspections to provide consistency in program and policy approaches. In addition, FDA plans to develop guidance on facility standards for biotechnology manufacturing facilities to clarify regulatory requirements and FDA policy.

5. One comment requested that companies have the option to submit descriptions of systems design, equipment validation, etc., for FDA review and comment prior to the time of inspection because it would be advantageous to both industry and FDA.

FDA agrees that the submission of facility information, such as systems design, and early dialogue is advantageous to both industry and FDA. Accordingly, the agency intends to continue to review this information, when requested, and provide comments early in the development process, prior to and after the submission of the license application. Companies should contact the Division of Establishment Licensing, CBER, to arrange such reviews.

6. One comment stated that the use of an interim definition of products that would be eligible for single license application under § 601.2(c) creates the possibility that FDA might refuse to file a biologics license application for a product that the applicant believes is well-characterized, even though the application might include sufficient data to demonstrate that the product meets prescribed standards for safety, purity, and potency. Another comment suggested that the determination as to whether a product is well-characterized should be made during the Phase 2 clinical trials or as early in the process as is practical.

As discussed above in the response to comment No. 1 of this document, FDA has decided to clearly identify, by category, those products subject to the rule, and thereby reduce uncertainty as to whether a product falls within the scope of the rule. This clear identification of products should also eliminate the concerns regarding a refusal to file action and the need to provide sufficient data to support an applicant's claim that its product is ''well-characterized.'' Applicants seeking licensure of a product that falls within a category listed in 601.2(c) will not be required to make an initial showing that the product is ''well-characterized'' to use the new procedures. Companies may seek guidance from FDA at any time on the type of application that should be submitted, and FDA encourages early communication.

7. One comment agreed with FDA's proposal to exempt well-characterized products from § 610.62, which sets out requirements for position and prominence of the proper name of the product on the package label. The comment suggested that this labeling change should be voluntary for currently licensed products, that companies should be allowed to phase in changes over a 24 month time period, and that preapproval should not be required.

The comment may have misunderstood the applicability of § 201.10(g) (21 CFR 201.10(g)). Section 201.10(g) applies to biological products licensed under section 351 of the PHS Act, as well as to drugs approved under the act. Accordingly, labels that comply with preexisting requirements should not require revisions to comply with the requirements in this final rule.

8. One comment suggested that manufacturers submitting a biologics license application should be permitted to cross-reference information already supplied in an approved ELA.

FDA agrees that avoiding unnecessary duplication of information in applications is desirable. FDA will permit a biologics license applicant to cross-reference information already submitted in an approved ELA at this time. However, the agency may reassess the viability of this approach in the future. Should the information in the approved ELA become outdated, cross-reference may no longer be appropriate.

9. One comment agreed with FDA's proposed revision of the definition of ''manufacturer'' in § 600.3(t). Three comments requested that FDA apply an expanded definition of ''manufacturer'' to all biologic license applicants and not limit application of this definition exclusively to well-characterized products. One of the comments favoring a broader definition suggested the following language for § 600.3(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 product, or a license holder, who is responsible for assuring that the product and establishment standards are met.

FDA agrees with the comments requesting the broader definition of ''manufacturer'' and is revising § 600.3(t) to include any license applicant who assumes responsibility for compliance with the applicable product and establishment standards in parts 600 through 680. FDA believes that this change will facilitate contract manufacturing arrangements for all biological products by allowing an applicant who does not own all the facilities where significant manufacturing is performed to apply for licensure. The revised § 600.3(t) will define ''manufacturer'' as the term is used in parts 600 through 680. Contract firms engaged in the manufacture, processing, packing, or holding of a biological drug will continue to be subject to applicable CGMP requirements and the amendment to § 600.3(t) will not affect other definitions of ''manufacturer'' contained in other applicable statutes and regulations. FDA intends to revise current guidance on contract manufacturing arrangements for applicants interested in pursuing such arrangements under the new definition.

10. One comment requested that § 610.63, which addresses package label and container label requirements for products manufactured under an arrangement involving two or more establishments, be exempted from applicability to well-characterized biotechnology products because such products would involve a single license holder. The comment suggested that it would be unnecessary to require that the labeling show the names of multiple participating manufacturers.

The agency does not agree that § 610.63 should be exempted from applicability to the products covered in this rule. Divided or shared manufacturing arrangements could still exist between holders of biologics licenses for products subject to this rule if this was an arrangement the companies desired, and in these cases § 610.63 would apply.

However, FDA agrees that it is unnecessary to identify contract

manufacturers on the package label and container label of a biological product subject to this final rule. FDA has applied § 610.63 to require label identification of licensed manufacturers only. As discussed below, FDA intends to consider the need for revisions to § 610.63 in separate rulemaking. FDA also intends to revise the November 25, 1992, Policy Statement Concerning Cooperative Manufacturing Arrangements for Licensed Biological Products to address contract, divided, and shared manufacturing arrangements under the new regulatory scheme.

11. One comment suggested that §§ 610.60, 610.61, 610.63, 610.64, and 610.65 be eliminated for all biologic products and be replaced by labeling requirements described in part 201 (21 CFR part 201), subpart A.

FDA agrees that harmonizing the labeling requirements for biologics and drugs approved under the act, where appropriate, is desirable. It is important to note that biologic products are already subject to most provisions in subpart A of part 201. FDA is considering revising the labeling requirements in §§ 610.60 through 610.65 as part of the agency's comprehensive review and rewrite of the general biologics regulations.

12. One comment stated that § 600.10(a), which describes the requirements for an establishments to designate a ''responsible head,'' should not apply to well-characterized products as currently written.

FDA agrees that § 600.10(a), as currently written, imposes unnecessary burdens for many modern biological manufacturers and has made a commitment to publish a proposed rule to revise this regulation within 9 months of the publication of the President's November, 1995, National Performance Review, ''Reinventing the Regulation of Drugs Made From Biotechnology.'' FDA intends to revise the requirements to allow more flexibility to assign control and oversight responsibility within a company.

13. One comment requested that § 600.22(g), which authorizes inspectors to inspect and copy, as circumstances may require, any records to be kept under to § 600.12, be amended because § 600.12 will not apply to well-characterized biotechnology products under this rule.

The agency believes that it is not necessary to amend § 600.22(g) because the CGMP requirements in parts 210 and 211 that apply to products subject to this rule include recordkeeping requirements and state that records are subject to photocopying as part of an FDA inspection (see § 211.180(b)).

14. One comment requested clarification of § 601.3(b), which describes the information required on the product license form. One comment requested that FDA eliminate the requirement for an establishment license number in the product license application (PLA) for well-characterized products because a contract manufacturing site engaged in multiproduct manufacture for different manufacturers may produce several licensed products. The comment stated that the establishment number would not be meaningful under such circumstances.

FDA believes that it is unnecessary to include an exemption for § 601.3(b)(4) in this rule. Elsewhere in this issue of the Federal Register, FDA is announcing the availability of an interim form, FDA 3439, which contains a section in which all locations performing manufacturing or testing of the product are to be identified. If a location has a license number, that number should be included as part of that identification, as should the location's registration number. If there is no license number for the location, it cannot be included, as is currently the case for a new establishment filing its first PLA and ELA.

15. One comment requested that § 601.22, which permits initial and partial manufacturing of products in short supply at other than a licensed establishment, be amended to include a statement clarifying the relevant referenced regulations when § 601.22 is applied to well-characterized products.

FDA agrees and is making conforming amendments to § 601.22 to specify that persons conducting the initial and partial manufacturing of a product that is subject to this rule shall be subject to all regulations of subchapter F except §§ 601.1 to 601.6, 601.9, 601.10, 601.20, 601.21; 601.30 to 601.33; 610.60 to 610.65, 600.10(b) and (c), 600.11, 600.12, 600.13, 610.11, and 610.53.

16. One comment stated that § 601.45, which requires, for certain products, submission of promotional materials to the agency, should not apply to well-characterized biotechnology products. The comment suggested that the proposed rule under which promotional labeling materials would not have to be submitted for agency consideration within 120 days following marketing approval be applied to well-characterized products. The comment also suggested that submission of advertisements and promotional labeling be regulated under § 314.81(b)(3)(i) (21 CFR 314.81(b)(3)(i)).

The comment may have misunderstood the applicability of § 601.45. Section 601.45 applies solely to biological products subject to subpart E, Accelerated Approval of Biological Products for Serious or Life Threatening Illnesses. For biological products not subject to subpart E, FDA has proposed to revise requirements for submission of advertisements and promotional labeling to CBER to reflect procedures found in § 314.81(b)(3)(i), in the proposal of January 29, 1996 (61 FR 2733 at 2739).

17. One comment requested that § 610.9, which permits manufacturers, under certain conditions, to modify a particular test method or manufacturing process, be exempted from applicability to well-characterized biotechnology products. The comment also suggested that this regulation be eliminated as part of the proposed revisions to § 601.12, published in the Federal Register (61 FR 2739).

FDA disagrees with the comment. The comment may have misunderstood § 610.9. This regulation allows manufacturers the flexibility to modify methods or processes specified in regulations, if the modification can be shown to provide equivalent assurance of safety, purity, potency, and effectiveness. Because this regulation adds flexibility without compromising the safety, purity, potency, or effectiveness of biological products, FDA believes that it should apply to all biological products.

18. One comment suggested that a broad interpretation of § 610.15, which describes the requirements for use of constituent materials, may require development of sophisticated purification methods to reduce the level of ''contaminating'' immunoglobulins to the one part per million level if applied to cell culture products such as monoclonal antibodies. The comment suggested that § 610.15 be amended to be applicable only to vaccine products and products intended to be antigenic.

Section 610.15(b) applies by its terms to cell culture-produced vaccines intended for injection. For guidance on the use of a serum in the medium for production of monoclonal antibodies, consult the Draft ''Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use,'' announced in the Federal Register of August 3, 1994 (59 FR 39571).

19. One comment suggested that § 600.81 (the comment references ''§ 601.81,'' but the subject is consistent with § 600.81), which describes the requirements for product distribution reports, is duplicative, provides no

value to the manufacturer or to FDA in ensuring the public health, and should be eliminated. The comment requested that distribution information for well-characterized biotechnology products be regulated under § 314.81(b)(2)(ii).

FDA disagrees with this comment. Section 600.81 differs from § 314.81(b)(2)(ii) in that § 600.81 requires submission of product distribution reports every 6 months; requires information on bulk lot number, fill lot number and label lot number; states that FDA may require more detailed information, as needed; and states that FDA may require, on written notice, submission of reports at times other than those stated in the regulation. FDA believes that the requirements in § 600.81 assist the agency in determining adverse reaction rates for vaccines and other biological products, and are of use in monitoring product safety. It should be noted that § 600.90 permits a licensed manufacturer to apply to FDA for a waiver from any of the requirements of § 600.81.

20. Several comments addressed issues beyond the scope of this rulemaking. Comments included issues related to reporting of errors and accidents (§ 600.14), lot release, methods for evaluating product characteristics, and establishing product specifications.

Revisions to § 600.14 *Reporting of errors* and other biologics regulations are currently under consideration and are outside the scope of this rulemaking. However, FDA will consider all comments received as a part of the agency's comprehensive rewrite of the general biologics regulations.

IV. Summary of Changes for the Final Rule

In response to comments received, FDA is making the following changes in this final rule:

In lieu of the term ''well-characterized biotechnology product,'' FDA is specifying, in § 601.2(a) (21 CFR 601.2(a)) and new paragraph (c), the categories of products to which the rule will be applicable, including therapeutic DNA plasmid products; therapeutic synthetic peptide products of 40 or fewer amino acids; monoclonal antibody products for in vivo use; and therapeutic recombinant DNA-derived products. The definition of manufacturer has been modified to include an applicant for a license for any biological product where the applicant assumes responsibility for compliance with the applicable product and establishment standards. The final rule also sets forth an amendment to 21 CFR 601.22 clarifying that section's applicability to the categories of products specified in new § 601.2(c).

V. Implementation Issues

Any therapeutic DNA plasmid product, therapeutic synthetic peptide product of 40 or fewer amino acids, monoclonal antibody product for in vivo use, and therapeutic recombinant DNA-derived product for which a PLA and an ELA are pending on the effective date of these regulations, will be reviewed as submitted. No new submission will be necessary to implement this rule change for these products. If found acceptable for licensure, FDA will issue a biologics license in lieu of issuing both a product and establishment license.

Applicants already holding an approved ELA and PLA for a product within the scope of this rule will not be required to file supplements to comply with the new requirements. The approved PLA for the product, together with the limited portions of the approved ELA relevant to the new requirements for the biologics license application, will be deemed to constitute an approved biologics license application under the new regulations.

The agency recognizes that there are a variety of contractual arrangements that could be affected by this rule. For example, an innovator company may have contracted with another company to make a product. Under the previous regulatory scheme, a contract manufacturer could hold both the establishment license and the product license. Under the new regulatory scheme, an innovator company may wish to hold the license. FDA anticipates that firms desiring an arrangement where the innovator holds the license could surrender the original licenses to the agency and request reissuance of a new biological license to the innovator under the provisions of this final rule. FDA urges license holders or those wishing to change their licensing arrangements to contact the agency for additional guidance on how this can be accomplished.

VI. Effective Date

The final rule is effective May 24, 1996. 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 will decrease the regulatory burdens for specified biotechnology and synthetic biological products, FDA believes that an immediate effective date is appropriate.

VII. Analysis of Impacts

A. Reduction in Burden

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

Companies developing and manufacturing products within the scope of this rule will no longer have to prepare an ELA to submit to the agency for approval. The amount of information that applicants will need to provide in a biologics license application will be less than that currently required in a PLA and ELA. These changes will 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 will 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 biotechnology product.

The inclusion of parts 210 and 211 in this final rule as establishment standards will not impose any additional burden on industry. Human drugs, including products subject to this rule, 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 final 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 final rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the final rule is a significant regulatory action as defined by the Executive Order and is subject to review under the Executive Order because it deals with a novel policy issue.

In accordance with the principles of Executive Order 12866, the overall result of the final rule will be a substantial reduction in burdens on

applicants filing for approval of a product subject to this rule. In addition, FDA anticipates that the final rule will 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 above, the overall result of the final rule will be a substantial reduction of the regulatory and reporting burdens, the agency certifies that the final rule will 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 final rule contains information collection requirements that were submitted for review and approval to the Director of the Office of Management and Budget (OMB) as required by section 3504(b) of the Paperwork Reduction Act of 1995. As part of this review, FDA provided individuals and organizations an opportunity to comment to OMB on the information collection requirements in the proposed rule. All comments received agreed that FDA's proposal to eliminate the ELA requirements for certain biotechnology products would reduce the burden to industry without diminishing the public health protection. As a result of information provided, FDA has revised the number of estimated applicants yearly from 1 to 15. The estimate for completing the application has not changed, however. This number remains at 40. These information collection requirements were approved and assigned OMB control number OMB No. 0910–0316. The expiration date for this approval is December 31, 1997. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

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.

Title: Elimination of Establishment License Application for Specified Biotechnology and Synthetic Biological Products.

Description: FDA is eliminating the requirement that an ELA be submitted and approved by FDA for specified biotechnology and synthetic biological 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 will be the same as the information included in the ''Chemistry, manufacturing, and controls'' (CMC) section of a new drug application. This regulation will harmonize the approval and other regulatory requirements applicable to specified biotechnology and synthetic biological products licensed under the PHS Act and drugs approved 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)	15	1	15	40	600

There are no capital costs or operating and maintenance costs associated with this information collection.

Reporting or Disclosure: These estimates are an approximation of the average time expected to be necessary for the collection of information. They are based on such information as is available to FDA.

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.

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, 21 CFR parts 600 and 601 are amended as follows:

PART 600—BIOLOGICAL PRODUCTS: GENERAL

1. 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).

2. 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 any legal person or entity who is an applicant for a license where the applicant assumes responsibility for compliance with the applicable product and establishment standards.

* * * * *

PART 601—LICENSING

3. 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).

4. Section 601.2 is amended by designating the text of paragraph (a) as introductory text of (a) and by adding a clause at the end of the introductory text, new paragraphs (a)(1) through (a)(4), and (c) to read as follows:

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

(a) * * * In lieu of the procedures described in this paragraph, applications for the following specified

categories of products shall be handled as set forth in paragraph (c) of this section:

(1) Therapeutic DNA plasmid products;

(2) Therapeutic synthetic peptide products of 40 or fewer amino acids;

(3) Monoclonal antibody products for in vivo use; and

(4) Therapeutic recombinant DNA-derived products.

* * * * *

(c)(1) To obtain marketing approval for a therapeutic DNA plasmid product, therapeutic synthetic peptide product of 40 or fewer amino acids, monoclonal antibody product for in vivo use, or therapeutic recombinant DNA-derived 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 products, a separate establishment license application shall not be required. An application for a license for such a product shall include:

(i) 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,

(ii) If the study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance;

(iii) 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;

(iv) A full description of manufacturing methods;

(v) Data establishing stability of the product through the dating period;

(vi) Sample(s) representative of the product to be sold, bartered, or exchanged or offered, sent, carried or brought for sale, barter, or exchange;

(vii) Summaries of results of tests performed on the lot(s) represented by the submitted samples; and

(viii) Specimens of the labels, enclosures, and containers proposed to be used for the product.

(2) 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.

(3) 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 a product subject to this paragraph (c) 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 such 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.

(4) The term ''product license application,'' as it is used in those sections of parts 600 through 680 of this chapter that are applicable to products subject to this paragraph (c) shall include a biologics license application for a therapeutic DNA plasmid product, therapeutic synthetic peptide product of 40 or fewer amino acids, monoclonal antibody product for in vivo use, or therapeutic recombinant DNA-derived product.

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

5. Section 601.22 is amended by adding a sentence after the second sentence to read as follows:

§ 601.22 Products in short supply; initial manufacturing at other than licensed establishment.

* * *For persons and places authorized under this section to conduct the initial and partial manufacturing of a product for shipment solely to a manufacturer of a product subject to licensure under § 601.2(c), the following additional regulations shall not be applicable: §§ 600.10(b) and (c), 600.11, 600.12, 600.13, 610.11, and 610.53 of this chapter * * *.

Dated: May 6, 1996.

William B. Schultz,

Deputy Commissioner for Policy.

[FR Doc. 96–12144 Filed 5–10–96; 10:13 am]

BILLING CODE 4160–01–F

DEPARTMENT OF TRANSPORTATION

Office of the Secretary

Coast Guard

33 CFR Part 52

[OST Docket No. OST–95–878]

RIN 2105–AC31

Coast Guard Board for Correction of Military Records; Procedural Regulation

AGENCY: Office of the Secretary, Coast Guard, DOT.

ACTION: Final Rule.

SUMMARY: The Department is amending its regulation with respect to reconsideration of final decisions of the Board for Correction of Military Records of the Coast Guard (BCMR). This action is taken on the Department's initiative in order to streamline processing of these cases and to clarify the circumstances under which final decisions can be reconsidered. The amendment will make it possible for the BCMR to expedite the processing of reconsideration requests and it will increase the resources available to meet the requirement that all cases be decided within 10 months of the receipt of a completed application.

EFFECTIVE DATE: June 13, 1996.

FOR FURTHER INFORMATION CONTACT: Robert H. Joost, Chairman, Board for Correction of Military Records of the Coast Guard, C–60, Office of the General Counsel, U.S. Department of Transportation, 400 Seventh Street, SW, Washington, D.C. 20590–0001. Telephone: (202) 366–9335.

SUPPLEMENTARY INFORMATION:

Comments on Proposed Rulemaking

Proposed rulemaking was published on pages 63489–63491 of the Federal Register of December 11, 1995 [60 FR 63489], and invited comments for 60 days ending February 9, 1996. Comments were received from the following sources: (1) Eugene R. Fidell, Esq., an attorney in private practice; and (2) Michael J. Calabro, Esq., an attorney in private practice. The comments and the actions taken in response to the comments are summarized below.

Both attorneys expressed concern with respect to the amount of time that