of the main entrance door required by paragraph (a) of this AD. Repeat the actions specified in paragraphs (b)(1) and (b)(2) of this AD, thereafter, at intervals not to exceed 1,500 hours time-in-service.

(1) Clean (remove contaminants and dry lubricant) and re-lubricate (with dry lubricant) the main entrance door ''speed'' lock and ''G'' lock systems in accordance with Jetstream Service Bulletin J41–52–058, dated July 14, 1997.

(2) Following accomplishment of paragraph (b)(1) of this AD and prior to further flight, perform a functional test of the main entrance door (including the ''G'' lock system) and the ''speed'' lock system, in accordance with the MM. If the ''G'' lock or ''speed'' lock system do not perform satisfactorily: Prior to further flight, repair the ''G'' lock or ''speed'' lock system in accordance with a method approved by the Manager, International Branch, ANM–116.

New Requirements of This AD:

(c) Within 60 days after the effective date of this AD, replace the ''G'' lock rollers on the main entrance door with new, improved ''G'' lock rollers in accordance with Jetstream Alert Service Bulletin J41–A–52–059, dated September 12, 1997, or Revision 2, dated January 23, 1998.

(d) An alternative method of compliance or adjustment of the compliance time that provides an acceptable level of safety may be used if approved by the Manager, International Branch, ANM–116. Operators shall submit their requests through an appropriate FAA Principal Maintenance Inspector, who may add comments and then send it to the Manager, International Branch, ANM–116.

Note 2: Information concerning the existence of approved alternative methods of compliance with this AD, if any, may be obtained from the International Branch, ANM–116.

(e) Special flight permits may be issued in accordance with sections 21.197 and 21.199 of the Federal Aviation Regulations (14 CFR 21.197 and 21.199) to operate the airplane to a location where the requirements of this AD can be accomplished.

Note 3: The subject of this AD is addressed in British airworthiness directive 001–09–97.

Issued in Renton, Washington, on July 24, 1998.

S. R. Miller,

Acting Manager, Transport Airplane Directorate, Aircraft Certification Service.

[FR Doc. 98–20430 Filed 7–30–98; 8:45 am]

BILLING CODE 4910–13–U

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 3, 5, 10, 20, 207, 310, 312, 316, 600, 601, 607, 610, 640, and 660

[Docket No. 98N–0144]

RIN 0910–AB29

Biological Products Regulated Under Section 351 of the Public Health Services Act; Implementation of Biologics License; Elimination of Establishment License and Product License

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 references to establishment licenses and product licenses for all products regulated under the Public Health Service Act (PHS Act). In lieu of filing an establishment license application (ELA) and product license application (PLA) in order to market a biological product in interstate commerce, a manufacturer would file a single biologics license application (BLA) with the agency. Upon approval of the BLA, a manufacturer would receive a biologics license to market the product in interstate commerce. This action is part of FDA's continuing effort to achieve the objectives of the President's ''Reinventing Government'' initiatives and is intended to reduce unnecessary burdens for industry without diminishing public health protection. This action also proposes regulations to implement certain sections of the Food and Drug Administration Modernization Act of 1997 (FDAMA).

DATES: Submit written comments by October 14, 1998. Submit written comments on the information collection requirements by August 31, 1998.

ADDRESSES: Submit written comments 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 Management and Budget (OMB), New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington, DC 20503.

FOR FURTHER INFORMATION CONTACT: Robert A. Yetter, Center for Biologics Evaluation and Research (HFM–10), Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448, 301–827–0373.

SUPPLEMENTARY INFORMATION:

I. Background

Currently, most manufacturers requesting approval to market a biological product in interstate commerce must submit a PLA and an ELA to FDA. FDA's Center for Biologics Evaluation and Research (CBER) currently requires manufacturers to use one of three ELA forms and 1 of 16 PLA forms for each biological product (see the **Federal Register** of July 8, 1997 (62 FR 36558)). Upon approval of the ELA and PLA, the agency issues a product license and an establishment license to the manufacturer. As discussed in the next three paragraphs, FDA has reviewed its process of licensing biological products and has already taken a number of actions to reduce the regulatory burdens imposed by the licensing process and to make the licensing process more consistent with the process for the approval of new drugs.

Manufacturers of certain biological products are already required to submit a BLA and obtain FDA approval of the BLA before the product may be introduced into interstate commerce. In the **Federal Register** of May 14, 1996 (61 FR 24227), FDA issued a final rule to amend the biologics regulations by eliminating the ELA requirement for specified biotechnology and synthetic biological products licensed under section 351 of the PHS Act (42 U.S.C. 262 *et seq.*). The specified biotechnology and synthetic biological products are: (1) Therapeutic deoxyribonucleic acid (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. This provision applies only to those products that FDA determines pursuant to principles articulated in the ''Intercenter Agreement Between the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research'' (effective on October 31, 1991) to be subject to licensure under Section 351 of the PHS Act. Thus, upon approval, manufacturers of the specified biotechnology and synthetic biological products receive a single biologics license instead of a product license and an establishment license (see § 601.2(c) (21 CFR 601.2(c))).

In the **Federal Register** of July 8, 1997 (62 FR 36558), FDA announced the availability of a revised FDA Form 356h. FDA Form 356h was revised as a ''Reinventing Government'' initiative to

harmonize application procedures with the Center for Drug Evaluation and Research (CDER) as outlined in the President's November 1995 National Performance Review Report, ''Reinventing the Regulation of Drugs Made From Biotechnology.'' FDA intended that applicants for biologics licenses for products specified in § 601.2(c) as well as autologous somatic cell therapy products could begin to use FDA Form 356h immediately and would be required to do so beginning January 8, 1998. FDA also intended to advise applicants for licenses for other biological products when they can voluntarily begin and will be required to use FDA Form 356h. Upon approval of a BLA submitted on FDA Form 356h, FDA will issue a single biologics license. FDA believes that this licensing procedure will greatly simplify the application process, harmonize application procedures with those of CDER, and reduce industry and agency paperwork burdens. FDA intends as a result of this proposed rule to require that all manufacturers requesting approval to introduce, or deliver for introduction, a biological product into interstate commerce use FDA Form 356h to submit a BLA in lieu of separate establishment and product applications.

With the consolidation of the establishment and product license applications into a single biologics license application, the amount of information formerly included in the establishment license application would be reduced but not eliminated. Some information formerly included in the ELA would now be submitted as ''chemistry, manufacturing, and controls'' (CMC) information and under the ''establishment description'' section of FDA Form 356h. The type and amount of information related to the establishment would vary according to the specific biological product for which licensure is being requested. To describe what information should be included for each type of biological product, CBER is preparing a series of guidance documents. Many of these guidance documents have already been made available, including but not limited to: (1) ''Guidance for Industry for the Submission of Chemistry, Manufacturing, and Controls Information for a Therapeutic Recombinant DNA-Derived Product or a Monoclonal Antibody Product for In Vivo Use'' (61 FR 56243, October 31, 1996); (2) ''Guidance for the Submission of Chemistry, Manufacturing, and Controls Information and Establishment Description for Autologous Somatic Cell Therapy Products'' (62 FR 1460, January 10, 1997); (3) ''Guidance for Industry for the Submission of Chemistry, Manufacturing and Controls Information for Synthetic Peptide Substances;'' and (4) ''Draft Guidance for Industry for the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Plasma-Derived Biological Product or Animal Plasma or Serum-Derived Products'' (63 FR 3145, January 21, 1998). All of these guidance documents can be downloaded from the CBER Guidelines/Guidance document World Wide Web page at ''www.fda.gov/cber/guidelines.htm''. These guidance documents can also be obtained by written request to the Office of Communication, Training, and Manufacturers Assistance (HFM–40), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448. Send one self-addressed adhesive label to assist the office in processing your requests. These documents may also be obtained by mail by calling the CBER Voice Information System at 1–800–835–4709 or 301–827–1800, or by fax by calling the FAX information System at 1–888–CBER–FAX or 301–827–3844. FDA intends in the future to announce in the **Federal Register** the availability of additional CMC guidance documents for various biological product classes.

II. Legal Authority

FDA licenses biological products under the authority of section 351(a) of the PHS Act. Although the PHS Act requires that biological products be licensed and be safe, pure, potent, and manufactured in facilities designed to assure that the product continues to be safe, pure, and potent; it does not mandate the number or form of licenses that FDA shall issued for each approvable biological product. The PHS Act also does not specify the license application forms that manufacturers must submit to FDA. Except for the biological products listed under § 601.2(c), FDA has required manufacturers to submit a PLA and an ELA for each biological product. Accordingly, upon approval, FDA issues two licenses for each product.

On November 21, 1997, the President signed into law the FDAMA (Public Law 105–115). Section 123 of FDAMA, in pertinent part, amended section 351 of the PHS Act to specify that a biologics license shall be in effect for a biological product prior to such product's introduction into interstate commerce. FDAMA thereby statutorily codified FDA's administrative BLA/biologics license ''Reinventing Government'' initiative. Section 123(a)(1) of FDAMA further states that the Secretary of Health and Human Services (delegated to the Commissioner of Food and Drugs, at 21 CFR 5.10(a)(5)) shall approve a ''biologics license application'' on the basis of a demonstration that the biological product that is the subject of the application is safe, pure, and potent; and the facility in which the biological product is manufactured, processed, packed, or held meets standards designed to ensure that the biological product continues to be safe, pure, and potent.

The regulatory standards for establishments manufacturing biological products can be found in the biologics regulations in parts 600 through 680 (21 CFR parts 600 through 680) and in the drug and device good manufacturing practice regulations in parts 210 and 211 (21 CFR parts 210 and 211). The licensed manufacturer must also adhere to product and establishment standards established and agreed upon in the biologics license application. These standards from applicable regulations and as established in licenses for different biological products, will continue to constitute the requirements for the approval of biologics licenses under section 123 of FDAMA. For consistency and to reduce confusion, FDA will continue to use the terms ''establishment'' and ''licensed establishment'' in the biologics regulations when referring to a place of manufacturing, processing, or packing instead of the term ''facility'' as used in section 123 of FDAMA. FDA is proposing to amend § 600.3(w) to make clear that the term ''establishment'' in the biologics regulations has the same meaning as ''facility'' in section 123 of FDAMA.

Section 123(a)(2) of FDAMA eliminated section 351(d) of the PHS Act that required licenses for the maintenance of establishments for the propagation or manufacture and preparation of biological products. Section 123(f) of FDAMA states that the Secretary of Health and Human Services shall take measures to minimize differences in the review and approval of products licensed under section 351 of the PHS Act and products approved through new drug applications (NDA's) under the Federal Food, Drug, and Cosmetic Act (the act).

Therefore, this proposal is intended to amend regulations in chapter 21 of the Code of Federal Regulations (CFR) in order to implement the regulatory changes concerning biologic license applications and biologics licenses in the PHS Act codified by FDAMA. This proposal would: (1) Amend the

regulations in chapter 21 CFR by eliminating almost all references to establishment and product applications and licenses and substituting the terms ''biologics license application'' and ''biologics license;'' (2) codify in the biologics regulations that FDA would issue a ''biologics license'' upon approval of a BLA; (3) require a manufacturer of a biological product to submit a BLA on FDA Form 356h to obtain approval of the license in order to market the product in interstate commerce; (4) harmonize application procedures with products approved under a NDA; and (5) update the format of certain regulations.

FDA believes that its administrative approach towards reviewing regulatory submissions under the PHS Act can and should evolve in response to changing technology, knowledge, and experience in reviewing the safety, purity, and potency of biological products.

III. Summary of Proposed Rule

A. Definition and Deletion of Terms

In order to reduce any confusion that may result from use of the term ''facility'' in section 351 of the PHS Act as amended by FDAMA, FDA is proposing to amend the definition of ''establishment'' in § 601.3(w) to include that the term has the same meaning as ''facility'' in section 351 of the PHS Act.

FDA is proposing to modify the definition of ''standards'' in § 600.3(n) to indicate that the term refers to specifications and procedures established in biologics license applications designed to insure the continued safety, purity, and potency of biological products as well as to specifications and procedures in applicable regulations. FDA has authority under Section 351 of the PHS Act to establish standards in the review and approval of BLA's. Section 351(d) of the PHS Act which previously stated that standards designed to insure the continued safety, purity, and potency of biological products be ''prescribed in regulations'' was removed by FDAMA. FDA believes that allowing standards to be established in the BLA will enable the manufacturer and FDA to keep pace with evolving science and technology. Establishing standards in the BLA is consistent with FDA's previous effort to streamline the license review process by deleting certain additional standards in the biologics regulations (see 61 FR 40153, August 1, 1996). This proposed change to § 600.3(n) would also reduce confusion in the biologics regulations by establishing consistency with FDA's current regulation at § 601.5(b)(4) regarding the revocation of licenses.

FDA is proposing to delete the term ''licensee'' as used in the biologics regulations in order to reduce confusion and to make clear the fact that it is the licensed manufacturer who is responsible for compliance with product and establishment requirements. The term ''licensed manufacturer'' would be inserted in all instances that currently read ''licensee.''

B. Elimination of PLA/ELA and Implementation of BLA

In the past, in order to help ensure that biological products were safe, pure, and potent, FDA, and prior to FDA, the U.S. Public Health Service believed that it was necessary to have both the biological product and the establishment in which it was manufactured licensed separately. In light of FDA's accumulated experience and expertise regulating biological products and due to technical advances that have significantly increased the ability of manufacturers to control and analyze the manufacture of biological products, FDA, and the biologics industry to a great extent, no longer find the separate licensing scheme for biological products and establishments to be necessary. After much consideration and in a ''Reinventing Government'' initiative to reduce burden on industry by implementing a single biologics licensing scheme, FDA had already begun drafting this proposal when FDAMA was signed into law on November 21, 1997. Section 123 of FDAMA in effect codifies FDA's BLA initiative by requiring that FDA issue a ''biologics license'' to a manufacturer that has submitted a BLA to FDA and has demonstrated in the agency's view that the product is and will be manufactured in a manner that ensures the product's continued safety, purity, and potency.

This proposal substitutes the terms ''biologics license'' or ''biologics license application'' in lieu of references to product and establishment applications and product and establishment licenses in all regulations in chapter 21 CFR. In a few instances references to product and establishment licenses would be retained for historical accuracy (e.g., §§ 601.25 and 601.26).

Under the proposed regulations, a manufacturer applying for approval to market a biological product under section 351 of the PHS Act would submit to FDA the appropriate establishment and product information on the recently approved FDA Form 356h (see 62 FR 36558). Manufacturers would no longer be required to submit product or establishment information on the many different PLA and ELA forms currently in use. Upon approval of the BLA, FDA would issue an approval letter that in general terms states that FDA hereby grants the licensed manufacturer a biologics license to manufacture the particular biological product. FDA would not issue license certificates separate from the approval letter as is current agency practice. The approval letter would serve as the functional equivalent of a biologics license within the meaning of section 351 of the PHS Act.

FDA is proposing in § 601.2(a) that manufacturers would list in the BLA the addresses of all locations of manufacture of a biological product. FDA believes this would simplify and clarify the licensing processes by having necessary establishment information in the BLA and also by allowing FDA to approve all locations involved in the manufacture of the product without having to issue an establishment license for each location.

FDA is proposing under § 601.9(c) that manufacturers of some biological products would be able to list multiple products in a BLA and FDA would be able to issue a single biologics license to the manufacturer for more than one product. FDA would most likely use this approach with products that have been on the market for a long period of time, and for which FDA has considerable knowledge and expertise regulating, such as blood and blood components and nonstandardized allergenic products (see sections III.E and III.F of this document).

C. Specified Products Outlined in Current § 601.2(c)

In order to continue harmonized review of specified biotechnology and specified synthetic biological products by CDER and CBER, the products outlined in the May 14, 1996, final rule (61 FR 24227) would continue to be exempt from regulations at §§ 600.10(b) and (c), 600.11, 600.12, 600.13, 610.11, 610.53, and 610.62.

D. Radioactive Biological Products

The agency believes that the regulations for the licensing of radioactive biological products under § 601.2(b) may be confusing to the industry and do not accurately reflect the current policies of CBER and CDER. FDA is therefore proposing to amend § 601.2(b) to clarify procedures for submitting an application for marketing approval for a radioactive biological product in order to help ensure consistency with current CBER and CDER policies and procedures. These proposed regulations are intended to merely clarify when a manufacturer of

a radioactive biological product should submit a NDA to CDER or a BLA to CBER and should not be construed as an attempt to address or implement the requirements of section 122 of FDAMA, ''Requirements for Radiopharmaceuticals.'' FDA intends in a separate rulemaking to issue proposed regulations regarding the approval of radiopharmaceuticals as required by section 122 of FDAMA. The proposed provision provides that when the biological component of a radioactive coupled antibody determines the site of action, normally a BLA should be submitted. The regulation provides sufficient flexibility to take into account situations that may arise in the future where the scientific issues associated with the radionuclide or other chemically synthesized component are more significant than the scientific issues associated with the biological component. In such cases jurisdiction will be determined in accordance with principles articulated in the ''Intercenter Agreement Between the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research'' effective on October 31, 1991.

E. Blood and Blood Components

Currently CBER requires manufacturers to use as many as 10 different forms for the submission of ELA's and PLA's for blood and blood components. In addition, the agency currently issues a product and establishment license for each of seven product types covered by the forms (e.g. Whole Blood, Platelets, Plasma, Red Blood Cells, Cryoprecipitate, Source Plasma). Under the proposed rule, the agency would require a manufacturer of blood and blood components participating in interstate commerce to use FDA Form 356h to request approval to market. However, a manufacturer of blood and blood components would only need to submit one BLA to request approval to market one or more blood or blood components (e.g. Whole Blood, Platelets, Plasma, Red Blood Cells, Cryoprecipitate, Source Plasma). FDA believes this consolidation of forms and submissions would result in a reduced regulatory burden for the blood industry because information previously duplicated in the many blood and blood component product and establishment applications would be submitted only once in the BLA.

In addition, the proposed BLA system would simplify submission of supplements to blood and blood component applications. Currently, manufacturers desiring to make a single manufacturing change that would affect multiple products are required to submit a supplement to each individual product and establishment application. Under this proposal a manufacturer would only need to submit one supplement to the BLA. For example, under the current PLA/ELA system if a manufacturer desired to make a single change to the irradiation procedure for its Whole Blood, Red Blood Cells, Platelets, and Plasma products manufactured at 3 locations, the manufacturer would be required to submit 12 supplements to 4 PLA's. Under the proposed BLA system, the manufacturer would only be required to submit one supplement to the BLA describing the change for all of the products and locations involved. FDA intends to continue to streamline the blood and blood components application process in the future as part of FDA's Reinvention of Blood Regulation initiative.

In vitro diagnostic kits (IVD's) and blood grouping reagents involving blood and blood products are often licensed as individual products under section 351 of the PHS Act. Unlike other blood and blood component products, applications to market IVD's and blood grouping reagents are unique and specific for each product. In order for FDA to evaluate the safety, purity, potency, and effectiveness of each IVD or blood grouping reagent, manufacturers submit detailed product and establishment information to FDA in the application to market the product. FDA would continue to evaluate IVD's and blood grouping reagents on an individual basis and would therefore require a BLA for each product. Accordingly, upon approval of the BLA, FDA would issue a single biologics license for each IVD or blood reagent grouping product.

F. Allergenic Products

A significant number of manufacturers of allergenic products manufacture many different types of non-standardized allergenic extracts for immunotherapeutic and/or diagnostic indications. Currently, a manufacturer of multiple non-standardized allergenic extract products holds a single product license for all of the non-standardized allergenic extracts manufactured by the firm. FDA estimates that requiring or issuing a biologics license for each type of non-standardized allergenic extract from each manufacturer would be burdensome to the allergenics industry and FDA. Therefore, in order to simplify application procedures and reduce burden on industry and FDA, under the BLA/biologics license scheme a manufacturer of multiple non-standardized allergenic extracts wishing to market these products in interstate commerce would only be required to submit a single BLA to the agency.

However, under this proposed rule, standardized allergenic products would be regulated as individual biological products. Therefore, a manufacturer that wishes to market single or multiple standardized allergenic products would be required to submit a single BLA for each standardized product because of the detailed product and establishment specifications necessary to manufacture such products.

Under proposed § 601.2(e) FDA is proposing that every manufacturer of biological products, including allergenic product manufacturers, holding an unsuspended and unrevoked product license and establishment license would be considered to have a biologics license. Thus, an allergenic manufacturer holding an establishment license and product license for multiple non-standardized allergenic extracts would be considered to have a single biologics license for those products. Likewise, a manufacturer holding an establishment license and product license for a single standardized allergenic extract would be considered to have a biologics license for that product.

G. Current Good Manufacturing Practice Requirements

The establishment requirements for biological products regulated under Section 351 of the PHS Act would continue to include the current good manufacturing practice (CGMP) regulations found in parts 210, 211, 600, 606, and 820 (21 CFR part 820). FDA would review compliance with CGMP's during inspections; applicants would be required to demonstrate such compliance in order to obtain a biologics license.

Under section 501(a)(2)(B) of the act (21 U.S.C. 351(a)(2)(B) *et seq.*) the methods used in, and the facilities or controls used for the manufacture, processing, packing, or holding of a drug must conform to CGMP. Because 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 CGMP. 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 specifically applicable to the manufacture of bulk drug components, there are numerous instances where CGMP, within the meaning of 501(a)(2)(B) of the act, for bulk drug

substances and bulk drug product components would parallel the requirements set forth in part 211 (see 43 FR 45076, September 29, 1978). Because biological products can be susceptible to contamination, adequate control over bulk manufacturing is important. FDA intends to use the requirements of part 211 during inspections of manufacturers of bulk biological drug substances and bulk biological drug product components, to help assure that biological products will have the proper raw materials controls, process validation and controls, and sensitive and validated test methods and specifications that are necessary to ensure the safety, purity, potency, and effectiveness of the product. The establishment requirements in §§ 600.10 through 600.15 and the inspection regulations in §§ 600.20 through 600.22 would continue to apply to all biological products licensed under section 351 of the PHS Act except for those exemptions allowed under § 601.2(c) for specified biotechnology and synthetic products. Therefore, for clarity and to reduce confusion FDA would make clear in new § 601.2(d) that the CGMP requirements in parts 210, 211, 600, 606, and 820 are included, as applicable, as part of the establishment requirements for the production of a biological product. FDA is currently reviewing the biological product licensing and inspection regulations in order to update them as part of CBER's review of general biologics and licensing regulations (see 59 FR 3043, January 20, 1994; and 59 FR 28821, June 3, 1994).

H. Required Use of FDA Form 356h

Manufacturers of the four classes of specified biotechnology products specified in § 601.2(c) are currently required to use FDA Form 356h when requesting permission to market one of these biological products in interstate commerce. Manufacturers of autologous somatic cell therapy products subject to licensure under section 351 of the PHS Act should also use FDA Form 356h. Manufacturers of other biological products should continue to use the current forms until such time as final CMC and establishment guidance documents are made available. Ten months after the effective date of any final rule based on this proposal, all manufacturers of biological products licensed under section 351 of the PHS Act would be required to use FDA Form 356h as the form prescribed for such purpose under § 601.2(a). Regardless of which form(s) has been submitted for application to market, CBER will begin issuing biologics licenses in lieu of establishment and product licenses for any biological product that is approved on and after February 19, 1998, the effective date of FDAMA.

IV. Administrative Implementation Issues

A. CBER Policy on Use of the Terms ''Licensed Establishment'' and ''Licensed Manufacturer''

In order to be clear, consistent, and reduce confusion that may result from the proposed BLA scheme, FDA will continue to use the terms ''licensed establishment'' and ''licensed manufacturer'' in the biologics regulations. Under the proposed BLA scheme there would be no establishment license issued along with an approved BLA, however, all establishments listed in the approved biologics license application as engaged in the manufacture of any part of the biological product or the whole biological product would be considered a licensed establishment under the biologics regulations (including contract manufacturers and short suppliers). FDA believes it is important to continue to use the term ''licensed establishment'' in the regulations in order to convey the importance of the establishment in the BLA scheme as FDA reviews, inspects and approves the establishment as part of the biologics license approval process.

The term ''licensed manufacturer'' as used to pertain to biological products regulated under section 351 of the PHS Act would continue to mean any legal person or entity holding an unsuspended and unrevoked biologics license and who is therefore ultimately responsible for compliance with all product and establishment requirements under the applicable regulations and agreed upon in the BLA. FDA believes it is important to continue to use the term ''licensed manufacturer'' in the biologics regulations in order to emphasize that the manufacturer must have a U.S. license number issued by FDA and must also hold a biologics license for the biological product.

B. Applications in Preparation

FDA recognizes that it may take applicants time to switch format from PLA's and ELA's to BLA's. Therefore, FDA proposes to continue to accept PLA's and ELA's in lieu of a BLA for 10 months after the effective date of a final rule based on this proposal. However, all applications submitted to the agency after the effective date of the final rule would be required to include all information indicated in FDA Form 356h in order for the application to be considered as filed by CBER. PLA's and ELA's received after the effective date of the final rule would be administratively handled by FDA as a BLA. Any manufacturer planning to file a PLA and an ELA during the 10-month time period after the effective date of these regulations should contact FDA for further guidance.

C. Applications Currently Under Review

FDA proposes that any biological products for which a PLA and an ELA are pending on the effective date of these regulations would be reviewed as submitted. Not withstanding the new regulations, new submissions by the manufacturer would not be necessary for these products. If the PLA and ELA are sufficient for licensure, FDA would issue a biologics license as required by section 351 of the PHS Act as amended by FDAMA.

D. PLA's and ELA's Currently in Effect

FDA proposes under new § 601.2(e) that a manufacturer already holding an approved ELA and PLA for a biological product would not be required to file supplements to comply with the amended regulations. The approved PLA together with portions of the approved ELA relevant to the new requirements for the BLA, would be deemed to constitute a biologics license under section 351 of the PHS Act .

E. BLA Tracking Number and U.S. License Number of the Manufacturer

1. BLA Tracking Number

Consistent with the proposed BLA scheme, FDA intends to use a new internal BLA tracking and numbering system to track applications, manufacturers, and approvals. Each biological product would be assigned a BLA tracking number at the time the BLA is submitted by the manufacturer. The BLA tracking number assigned by CBER upon receipt of a BLA would remain indefinitely associated with the biological product. Use of the BLA tracking number would be similar to the use of the NDA number for drugs approved under section 505(b) of the act (21 U.S.C. 355(b)). After publication of a final rule based on this proposal, CBER intends to assign a BLA tracking number to each currently approved application and notify each licensed manufacturer of their respective BLA tracking numbers. Licensed manufacturers will be requested to use the BLA tracking number in all correspondence to the agency concerning a particular biological product.

2. U.S. License Number of the Manufacturer

FDA issues biologics licenses (U.S. licenses) to new manufacturers of biological products. Upon approval of a BLA, a manufacturer if not previously licensed would receive a U.S. license number that is required under section 351 of the PHS Act to appear on the label of the biological product. The U.S. license number would also be used to satisfy all regulatory requirements regarding ''license numbers'' and in all of the same instances that the ''establishment license number'' is currently used by industry and CBER. A manufacturer already holding a U.S. license number from CBER on the effective date of any final regulations would continue to use its current U.S. license number as required in the biologics regulations.

FDA would NOT issue a separate ''biologics license number'' with the approval of each biological product. In summary: (1) The biologics tracking number would be assigned by FDA when the BLA is filed, it would stay with the biological product for its life, and it would be used on all correspondence regarding the product; (2) the U.S. license number would be assigned to each manufacturer (if not already holding one) at the time of licensure of a biological product and would be used on all of the manufacturer's labeling for approved biological products; and (3) the approval letter for each biological product would serve as the biologics license under section 351 of the PHS Act.

F. CMC and Establishment Information Guidance

As stated earlier in this proposed rule, CBER has made available certain guidance documents that outline the recommended information to be provided in the CMC and establishment sections of FDA Form 356h. Biological product classes for which CBER is currently drafting CMC and establishment information guidance documents include but are not limited to: Vaccines, allergenic products, in vitro diagnostic products, therapeutic plasmid DNA products, therapeutic naturally-derived protein products, human plasma and animal serum derived products, and human blood and blood component products. As these guidance documents are completed and made available for various biological products, FDA will encourage manufacturers to begin to use Form FDA 356h. FDA intends to make CMC and establishment information guidance documents available for all biological product classes by the time a final rule on this subject is published. The CMC guidance documents are intended to help manufacturers comply with product and establishment requirements in applicable regulations including but not limited to parts 210, 211, 600, 601, 606, and 820.

G. Public Meeting

FDA intends to hold a public workshop during the comment period of this proposed rule to discuss the BLA/biologics license scheme. The date, time, and location of the meeting will be announced in a document in a future issue of the **Federal Register**.

V. Proposed Effective Date

FDA proposes that a final rule resulting from this proposal become effective 60 days after its date of publication in the **Federal Register**. FDA understands that considerable resources are committed to the preparation of applications and therefore would continue to accept applications in the current two application format for 10 months after the effective date of any final rule based on this proposal. However, after the effective date of the final rule all information indicated in FDA Form 356h must be submitted in these submissions in order for the application to be considered by CBER as complete. Applications submitted in the current two application format after the effective date of the final rule will be administratively handled by FDA as a BLA. After the 10-month grace period FDA would no longer accept the two application format (ELA and PLA) and would only accept for filing BLA's submitted on FDA Form 356h.

VI. Analysis of Impacts

A. Reduction in Burden

The proposed harmonized use of FDA form 356h for all biological products and drugs regulated by CBER and CDER would reduce burden on industry by enabling manufacturers to submit applications for biological products and drugs in a consistent format.

Manufacturers intending to introduce biological products into interstate commerce would no longer have to prepare a PLA and an ELA to submit to the agency for approval. The amount of information that manufacturers would need to provide in a BLA would be less than that currently required in a PLA and ELA. These proposed changes would enable manufacturers to devote fewer resources to submitting documentation to the agency. Much of the information currently reviewed in an ELA at FDA headquarters would be reviewed at the manufacturing site during a preapproval inspection. According to many biological product manufacturers, preparation, submission, and approval of a separate PLA and ELA for each biological product adds substantially to the cost of licensing the product.

The inclusion of parts 210, 211, 600, 606, and 820 in the proposed rule as establishment requirements would only serve to clarify existing requirements and would not impose any additional burden on industry. Human drugs, including biological products regulated under section 351 of the PHS Act, are already subject to the CGMP's in parts 210, 211, 600, 606, and 820.

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 (5 U.S.C. 601–612). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impact; and equity). The agency believes that this proposed rule is consistent with the regulatory philosophy and principles identified in Executive Order 12866. In addition, the proposed rule is a significant regulatory action as defined in Executive Order 12866 and is subject to review 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 a manufacturer filing an application to market a biological product. In addition, FDA anticipates that the proposed rule would facilitate a manufacturer's ability to improve its licensed products and methods of manufacture by decreasing the burden and cost associated with filing applications and supplements.

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 substantial reduction in 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. The Paperwork Reduction Act of 1995

This proposed rule contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the PRA (44 U.S.C. 3501–3520). A description of these provisions is shown below with an estimate of the annual reporting burden. Included in the estimate is the time for reviewing the instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each 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: Biological Products Regulated Under Section 351 of the Public Health Service Act; Implementation of Biologics License; Elimination of Establishment License and Product License.

Description: FDA is proposing to revise the regulations regarding the procedures for application for approval to market a biological product regulated under section 351 of the PHS Act. Currently, most manufacturers must submit an ELA and a PLA when requesting approval to market a biological product in interstate commerce. Under the proposed regulations, a manufacturer would submit to FDA the appropriate establishment and product information in a single BLA in lieu of filing a separate ELA and PLA. The BLA is intended to replace the many different ELA and PLA forms currently in use. Upon approval of the BLA, a manufacturer would receive a single biologics license to market the product in interstate commerce.

Description of Respondents: Manufacturers of biological products.

The proposed rule amends the regulations for filing an application to market a biological product under § 601.2 to eliminate references to establishment licenses and product licenses for all products regulated under the PHS Act. The proposed rule would require biologics manufacturers to file a single BLA, rather than either an ELA or PLA, to market a biological product. The agency estimates that the total paperwork burden for manufacturers filing one application that consolidates the information currently required under both the PLA and ELA will net a decrease of approximately 10 percent. The estimate reduces the number of annual responses from a combined PLA/BLA/ELA total of 76 to a BLA total of 60. This estimate is derived from the total number of license applications received by FDA in fiscal year 1997 (76) minus the total number of ELA's filed in the same period (17). Based on information provided by industry, the time estimated to prepare an application for FDA approval to market a product is approximately 1,600 hours. In addition to § 601.2, there are other regulations included in the proposed rule that relate to certain information to be included in a license application including §§ 640.21(c), 640.22(c), 640.65(a), and 660.21(a)(3) and (d). The information collection requirements in the preceding regulations are included in the burden estimate below for § 601.2.

The proposed regulation also makes several technical amendments to conform the language throughout the biological product regulations to the changes proposed here for § 601.2. Specifically, the proposed rule makes the following technical term changes: References to product and establishment license, and product and establishment applications are replaced with ''biologics license'' or ''biologics license application;'' ''licensee'' is replaced with ''licensed manufacturer;'' and ''licensed establishments'' is replaced with ''licensed manufacturer.'' These technical changes impact neither the substantive requirements nor the paperwork burden of these regulations, each of which carry separate OMB clearance numbers as follows: §§ 207.20(c) and 207.21(a) (0910–0045); 600.80(c)(2) (0910–0308); 601.25(b)(3) (0910–0039); 607.20(b) and 607.21 (0910–0052); 610.63 and 640.71(b)(1) (0910–0116).

The following regulations relate to the submission of additional information in a supplement to a BLA. Sections 600.15(b) and 610.53(d) require submission of a request for an exemption or modification regarding the temperature requirements during shipment and from dating periods, respectively, for certain biological products. The preparation of an exemption request is estimated to be 8 hours; however, no requests were received by the agency under either regulations in fiscal year 1997. To account for the rare instance in which a request for an exemption may be made, the agency has estimated one respondent per year in Table 1. Section 640.6 requires that an applicant submit a request to make a certain modification of Whole Blood. The number of any supplement relating to Whole Blood filed by an applicant in fiscal year 1997 totaled 74. Because the agency could not determine the number of supplements filed specific to § 640.6, the estimate below is based on last year's total number of supplements related to Whole Blood.

The remaining regulations, §§ 640.21(c), 640.22(c), 640.64(c), and 640.74(a) and (b)(2), refer to information that is collected under § 601.12, under which the collection of information burden is calculated. Moreover, the proposed rule would make only technical changes to these regulations. For example, the term ''product license'' is changed to ''biologics licence,'' and the term ''product licensee'' is changed to ''licensed manufacturer.''

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN[1]

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
601.2	60	1	60	1,600	96,000
600.15(b)	1	1	1	8	8
610.53(d)	1	1	1	8	8
640.6	74	1	74	8	592

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

In compliance with section 3507(d) of the PRA (44 U.S.C. 3507(d)), the agency has submitted the information collection provisions of this proposed rule to OMB for review. Interested persons are requested to send written comments regarding information collection by August 31, 1998, 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.

D. Environmental Impact

The agency has determined under 21 CFR 25.30 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 October 14, 1998, 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. 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 3

Administrative practice and procedure, Biologics, Drugs, Medical devices.

21 CFR Part 5

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

21 CFR Part 10

Administrative practice and procedure, News media.

21 CFR Part 20

Confidential business information, Courts, Freedom of information, Government employees.

21 CFR Part 207

Drugs, Reporting and recordkeeping requirements.

21 CFR Part 310

Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and recordkeeping requirements.

21 CFR Part 312

Drugs, Exports, Imports, Investigations, Labeling, Medical research, Reporting and recordkeeping requirements, Safety.

21 CFR Part 316

Administrative practice and procedure, Drugs, Reporting and recordkeeping requirements.

21 CFR Part 600

Biologics, Reporting and recordkeeping requirements.

21 CFR Part 601

Administrative practice and procedure, Biologics, Confidential business information.

21 CFR Part 607

Blood.

21 CFR Parts 610 and 660

Biologics, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 640

Blood, Labeling, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR parts 3, 5, 10, 20, 207, 310, 312, 316, 600, 601, 607, 610, 640, and 660 be amended to read as follows:

PART 3—PRODUCT JURISDICTION

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

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 357, 360, 360c–360f, 360h–360j, 360gg–360ss, 371(a), 379e, 381, 394; 42 U.S.C. 216, 262.

2. Section 3.2 is amended by revising paragraph (k) to read as follows:

§ 3.2 Definitions.

* * * * *

(k) *Premarket review* includes the examination of data and information in an application for premarket review described in sections 505, 507, 510(k), 513(f), 515, or 520(g) or 520(l) of the act or section 351 of the Public Health Service Act of data and information contained in any investigational new drug (IND) application, investigational device exemption (IDE), new drug application (NDA), antibiotic application, biologics license application, device premarket notification, device reclassification petition, and premarket approval application (PMA).

* * * * *

PART 5—DELEGATIONS OF AUTHORITY AND ORGANIZATION

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

Authority: 5 U.S.C. 504, 552, App. 2; 7 U.S.C. 138a, 2271; 15 U.S.C. 638, 1261–1282, 3701–3711a; 15 U.S.C. 1451–1461; 21 U.S.C. 41–50, 61–63, 141–149, 321–394, 467f, 679(b), 801–886, 1031–1309; 35 U.S.C. 156; 42 U.S.C. 241, 242, 242a, 242l, 242n, 243, 262, 263, 264, 265, 300u–300u–5, 300aa–1; 1395y, 3246b, 4332, 4831(a), 10007–10008; E.O. 11921, 41 FR 24294, 3 CFR, 1977 Comp., p. 124–131; E.O. 12591, 52 FR 13414, 3 CFR, 1988 Comp., p. 220–223.

4. Section 5.58 is amended by revising paragraph (a)(3) to read as follows:

§ 5.58 Orphan products.

(a) * * *

(3) Applications for biologics licenses for biological products; or

* * * * *

5. Section 5.67 is amended by revising paragraphs (a), (b), and (c) to read as follows:

§ 5.67 Issuance of notices of opportunity for a hearing on proposals for denial of approval of applications for licenses or revocation of licenses and certain notices of revocation of licenses.

* * * * *

(a) Notices of opportunity for a hearing on proposals to deny approval or filing of applications for biologics licenses under § 601.4(b) of this chapter.

(b) Notices of opportunity for a hearing on proposals to revoke biologics licenses under § 601.5(b) of this chapter.

(c) Notices of revocation, at the manufacturer's request, of biologics licenses under §§ 601.5(a) and 601.8 of this chapter.

* * * * *

PART 10—ADMINISTRATIVE PRACTICES AND PROCEDURES

6. The authority citation for 21 CFR part 10 is revised to read as follows:

Authority: 5 U.S.C. 551–558, 701–706; 15 U.S.C. 1451–1461; 21 U.S.C. 141–149, 321–397, 467f, 679, 821, 1034; 28 U.S.C. 2112; 42 U.S.C. 201, 262, 263b, 264.

7. Section 10.50 is amended by revising paragraph (c)(19) to read as follows:

§ 10.50 Promulgation of regulations and orders after an opportunity for a formal evidentiary public hearing.

* * * * *

(c) * * *

(19) Section 351(a) of the Public Health Service Act on a biologics license for a biological product.

* * * * *

PART 20—PUBLIC INFORMATION

8. The authority citation for 21 CFR part 20 is revised to read as follows:

Authority: 5 U.S.C. 552; 18 U.S.C. 1905; 19 U.S.C. 2531–2582; 21 U.S.C. 321–393, 1401–1403; 42 U.S.C. 241, 242, 242a, 242l, 242n, 243, 262, 263, 263b–263n, 264, 265, 300u–300u–5, 300aa–1.

9. Section 20.100 is amended by revising paragraph (c)(24) to read as follows:

§ 20.100 Applicability; cross-reference to other regulations.

* * * * *

(c) * * *

(24) Applications for biologics licenses for biological products, in § 601.51 of this chapter.

* * * * *

PART 207—REGISTRATION OF PRODUCERS OF DRUGS AND LISTING OF DRUGS IN COMMERCIAL DISTRIBUTION

10. The authority citation for 21 CFR part 207 continues to read as follows:

Authority: 21 U.S.C. 331, 351, 352, 355, 357, 360, 360b, 371, 374; 42 U.S.C. 262.

11. Section 207.20 is amended by revising paragraph (c) to read as follows:

§ 207.20 Who must register and submit a drug list.

* * * * *

(c) Before beginning manufacture or processing of a drug subject to one of the following applications, an owner or operator of an establishment is required to register before the agency approves it: A new drug application, a new animal drug application, a medicated feed application, an antibiotic application, or a biologics license application.

* * * * *

12. Section 207.21 is amended by revising the second sentence of paragraph (a) to read as follows:

§ 207.21 Times for registration and drug listing.

(a) * * * If the owner or operator of the establishment has not previously entered into such an operation, the owner or operator shall register within 5 days after submitting a new drug application, new animal drug application, medicated feed application, antibiotic application, or a biologics license application. * * *

* * * * *

PART 310—NEW DRUGS

13. The authority citation for 21 CFR part 310 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 357, 360b–360f, 360j, 361(a), 371, 374, 375, 379e; 42 U.S.C. 216, 241, 242(a), 262, 263b–263n.

14. Section 310.4 is revised to read as follows:

§ 310.4 Biologics; products subject to license control.

(a) Except for radioactive biological products intended for human use as described in § 601.2(b) of this chapter, a new drug shall not be deemed to be subject to section 505 of the act if it is a drug licensed under section 351 of the Public Health Service Act (42 U.S.C. 262 *et seq.*) or under the animal virus, serum, and toxin law of March 4, 1913 (21 U.S.C. 151 *et seq.*).

(b) A radioactive biological product (as defined in § 600.3(ee) of this chapter) intended for human use, except as identified in § 601.2(b)(1) of this chapter, is subject to section 505 of the act. Any license for such a radioactive biological product which was issued under section 351 of the Public Health Service Act (42 U.S.C. 262 *et seq.*) and which was not revoked or suspended as of August 25, 1975, shall constitute an approved new drug application in effect under the same terms and conditions as set forth in such license application and such portions of the establishment license relating to such product, which include data and information required under part 314 of this chapter for a new drug application. Any such radioactive biological product for which licensure under the Public Health Service Act was pending on August 25, 1975, shall, upon determination that it is acceptable for licensure, be approved as a new drug application in lieu of issuance of a biological product license.

15. Section 310.503 is amended by revising the first sentence of paragraph (b) to read as follows:

§ 310.503 Requirements regarding certain radioactive drugs.

* * * * *

(b) It is the opinion of the Nuclear Regulatory Commission, and the Food and Drug Administration that this exemption should not apply for certain specific drugs and that these drugs should be appropriately labeled for uses for which safety and effectiveness can be demonstrated by new drug applications or through licensing under the Public Health Service Act (42 U.S.C. 262 *et seq.*) in the case of biologics. * * *

* * * * *

PART 312—INVESTIGATIONAL NEW DRUG APPLICATION

16. The authority citation for 21 CFR part 312 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 357, 371; 42 U.S.C. 262.

17. Section 312.3 is amended in paragraph (b) by revising the definition for *Marketing application* to read as follows:

§ 312.3 Definitions and interpretations.

* * * * *

(b) * * *

Marketing application means an application for a new drug submitted under section 505(b) of the act, a request to provide for certification of an antibiotic submitted under section 507 of the act, or a biologics license application for a biological product submitted under the Public Health Service Act.

* * * * *

PART 316—ORPHAN DRUGS

18. The authority citation for 21 CFR part 316 continues to read as follows:

Authority: 21 U.S.C. 360aa, 360bb, 360cc, 360dd, 371.

19. Section 316.3 is amended by revising paragraph (b)(9) to read as follows:

§ 316.3 Definitions.

* * * * *

(b) * * *

(9) *Marketing application* means an application for approval of a new drug filed under section 505(b) of the act, a request for certification of an antibiotic under section 507 of the act, or an application for a biologics license submitted under section 351 of the Public Health Service Act (42 U.S.C. 262).

* * * * *

PART 600—BIOLOGICAL PRODUCTS: GENERAL

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

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 360i, 371, 374; 42 U.S.C. 216, 262, 263, 263a, 264, 300aa–25.

21. Section 600.3 is amended by revising paragraph (n) and (w) to read as follows:

§ 600.3 Definitions.

* * * * *

(n) The word *standards* means specifications and procedures applicable to an establishment or to the manufacture or release of products, which are prescribed in this subchapter

or established in the biologics license application designed to insure the continued safety, purity, and potency of such products.

* * * * *

(w) *Establishment* has the same meaning as ''facility'' in section 351 of the Public Health Service Act and includes all locations.

* * * * *

22. Section 600.15 is amended by revising paragraph (b) to read as follows:

§ 600.15 Temperatures during shipment.

* * * * *

(b) *Exemptions.* Exemptions or modifications shall be made only upon written approval, in the form of a supplement to the biologics license application, approved by the Director, Center for Biologics Evaluation and Research.

23. Section 600.21 is amended by revising the first sentence to read as follows:

§ 600.21 Time of inspection.

The inspection of an establishment for which a biologics license application is pending need not be made until the establishment is in operation and is manufacturing the complete product for which a biologics license is desired. * * *

24. Section 600.80 is amended by revising the first sentence of paragraph (b), the first and second sentences of paragraph (c)(2)(i), and by revising paragraphs (g) and (j) to read as follows:

§ 600.80 Postmarketing reporting of adverse experiences.

* * * * *

(b) *Review of adverse experiences.* Any person having a biologics license under § 601.20 of this chapter shall promptly review all adverse experience information pertaining to its product obtained or otherwise received by the licensed manufacturer from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers. * * *

* * * * *

(c) * * *

(2) *Periodic adverse experience reports.* (i) The licensed manufacturer shall report each adverse experience not reported under paragraph (c)(1)(i) of this section at quarterly intervals, for 3 years from the date of issuance of the biologics license, and then at annual intervals. The licensed manufacturer shall submit each quarterly report within 30 days of the close of the quarter (the first quarter beginning on the date of issuance of the biologics license) and each annual report within 60 days of the anniversary date of the issuance of the biologics license. * * *

* * * * *

(g) *Multiple reports.* A licensed manufacturer should not include in reports under this section any adverse experience that occurred in clinical trials if they were previously submitted as part of the biologics license application. If a report refers to more than one biological product marketed by a licensed manufacturer, the licensed manufacturer should submit the report to the biologics license application for the product listed first in the report.

* * * * *

(j) *Revocation of biologics license.* If a licensed manufacturer fails to establish and maintain records and make reports required under this section with respect to a licensed biological product, FDA may revoke the biologics license for such a product in accordance with the procedures of § 601.5 of this chapter.

* * * * *

PART 601—LICENSING

25. The authority citation for 21 CFR part 601 is revised to read as follows:

Authority: 15 U.S.C. 1451–1461; 21 U.S.C. 321, 351, 352, 353, 355, 360, 360c–360f, 360h–360j, 371, 374, 379e, 381; 42 U.S.C. 216, 241, 262, 263.

§ 601.1 [Removed]

26. Section 601.1 *Two forms of licenses* is removed.

27. Section 601.2 is revised to read as follows:

§ 601.2 Applications for biologics licenses; procedures for filing.

(a) *General.* To obtain a biologics license under section 351 of the Public Health Service Act for any biological product, the manufacturer shall submit an application to the Director, Center for Biologics Evaluation and Research, on forms prescribed for such purposes, and shall submit data derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed requirements 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, 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 sample(s); specimens of the labels, enclosures, and containers proposed to be used for the product and; the address of each location involved in the manufacture of the biological product shall be listed in the biologics license application. An application for a biologics license shall not be considered as filed until all pertinent information and data have been received from the manufacturer by the Center for Biologics Evaluation and Research. The applicant shall also include either a claim for categorical exclusion under § 25.30 or § 25.31 of this chapter or an environmental assessment under § 25.40 of this chapter. In lieu of the procedures described in this paragraph, applications for radioactive biological products shall be handled as set forth in paragraph (b) of this section. The applicant, or the applicant's attorney, agent, or other authorized official shall sign the application. An application for any of the following specified categories of biological products subject to licensure 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.

(b) *Radioactive biological products.* To obtain marketing approval for a radioactive biological product, as defined in § 600.3(ee) of this chapter, the manufacturer of such product shall comply with the following:

(1) An applicant for a radioactive coupled antibody, which means a product that consists of an antibody component coupled with a radionuclide component (or an antibody component intended solely to be coupled with a radionuclide) in which both components provide a pharmacological effect but the biological component determines the site of action, shall

submit a biologics license application to the Director, Center for Biologics Evaluation and Research, Food and Drug Administration, except if, as determined by FDA, there are significant scientific issues associated with the radionuclide or other chemically synthesized component, in which case a new drug application shall be submitted to the Center for Drug Evaluation and Research, Food and Drug Administration;

(2) An applicant for a radioactive biological product other than as described in paragraph (b)(1) of this section, shall submit a new drug application to the Center for Drug Evaluation and Research, Food and Drug Administration.

(c)(1) To obtain marketing approval for a biological product subject to licensure which is 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 a biologics license application in accordance with paragraph (a) of this section except that 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, 610.11, 610.53, and 610.62 of this chapter.

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

(d) Approval of a biologics license application or issuance of a biologics license shall constitute a determination that the establishment(s) and the product meet applicable requirements to ensure the continued safety, purity, and potency of such products. Applicable requirements for the maintenance of establishments for the manufacture of a product subject to this section shall include but not be limited to the good manufacturing practice requirements set forth in parts 210, 211, 600, 606, and 820 of this chapter.

(e) Any establishment and product license for a biological product issued under section 351 of the Public Health Service Act (42 U.S.C. 201 *et seq.*) that has not been revoked or suspended as of (insert effective date of final rule), shall constitute an approved biologics license application in effect under the same terms and conditions set forth in such product license and such portions of the establishment license relating to such product.

§ 601.3 [Removed]

28. Section 601.3 *License forms* is removed.

29. Section 601.4 is amended by revising paragraph (a) and the first sentence of paragraph (b) to read as follows:

§ 601.4 Issuance and denial of license.

(a) A biologics license shall be issued upon a determination by the Director, Center for Biologics Evaluation and Research that the establishment(s) and the product meet the applicable requirements established in this chapter. A biologics license shall be valid until suspended or revoked.

(b) If the Commissioner, determines that the establishment or product does not meet the requirements established in this chapter, the biologics license application shall be denied and the applicant shall be informed of the grounds for, and of an opportunity for a hearing on, the decision. * * *

30. Section 601.5 is revised to read as follows:

§ 601.5 Revocation of license.

(a) A biologics license shall be revoked upon application of the manufacturer giving notice of intention to discontinue the manufacture of all products manufactured under such license or to discontinue the manufacture of a particular product for which a license is held and waiving an opportunity for a hearing on the matter.

(b)(1) The Commissioner shall notify the licensed manufacturer of the intention to revoke the biologics license, setting forth the grounds for, and offering an opportunity for a hearing on, the proposed revocation if the Commissioner finds any of the following:

(i) Authorized Food and Drug Administration employees after reasonable efforts have been unable to gain access to an establishment or a location for the purpose of carrying out the inspection required under § 600.21 of this chapter,

(ii) Manufacturing of products or of a product has been discontinued to an extent that a meaningful inspection or evaluation cannot be made,

(iii) The manufacturer has failed to report a change as required by § 601.12,

(iv) The establishment or any location thereof, or the product for which the license has been issued, fails to conform to the applicable standards established in the license and in this chapter designed to ensure the continued safety, purity, and potency of the manufactured product,

(v) The establishment or the manufacturing methods have been so changed as to require a new showing that the establishment or product meets the requirements established in this chapter in order to protect the public health, or

(vi) The licensed product is not safe and effective for all of its intended uses or is misbranded with respect to any such use.

(2) Except as provided in § 601.6 or in cases involving willfulness, the notification required in this paragraph shall provide a reasonable period for the licensed manufacturer to demonstrate or achieve compliance with the requirements of this chapter, before proceedings will be instituted for the revocation of the license. If compliance is not demonstrated or achieved and the licensed manufacturer does not waive the opportunity for a hearing, the Commissioner shall issue a notice of opportunity for hearing on the matter under § 12.21(b) of this chapter.

31. Section 601.6 is revised to read as follows:

§ 601.6 Suspension of license.

(a) Whenever the Commissioner has reasonable grounds to believe that any of the grounds for revocation of a license exist and that by reason thereof there is a danger to health, the Commissioner may notify the licensed manufacturer that the biologics license is suspended and require that the licensed manufacturer do the following:

(1) Notify the selling agents and distributors to whom such product or products have been delivered of such suspension, and

(2) Furnish to the Director, Center for Biologics Evaluation and Research, complete records of such deliveries and notice of suspension.

(b) Upon suspension of a license, the Commissioner shall either:

(1) Proceed under the provisions of § 601.5(b) to revoke the license, or

(2) If the licensed manufacturer agrees, hold revocation in abeyance pending resolution of the matters involved.

32. Section 601.9 is revised to read as follows:

§ 601.9 Licenses; reissuance.

(a) *Compliance with requirements.* A biologics license, previously suspended or revoked, may be reissued or reinstated upon a showing of compliance with requirements and upon such inspection and examination as may be considered necessary by the Director, Center for Biologics Evaluation and Research.

(b) *Exclusion of noncomplying location.* A biologics license, excluding a location or locations that fail to

comply with the requirements in this chapter, may be issued without further application and concurrently with the suspension or revocation of the license for noncompliance at the excluded location or locations.

(c) *Exclusion of noncomplying product(s).* In the case of multiple products included under a single biologics license application, a biologics license may be issued, excluding the noncompliant product(s), without further application and concurrently with the suspension or revocation of the biologics license for a noncompliant product(s).

§ 601.10 [Removed]

33. Section 601.10 *Establishment licenses; issuance and conditions* is removed.

34. Section 601.20 is revised to read as follows:

§ 601.20 Biologics licenses; issuance and conditions.

(a) *Examination—compliance with requirements.* A biologics license application shall be approved only upon examination of the product and upon a determination that the product complies with the standards established in biologics license application and the requirements prescribed in the regulations in this chapter including but not limited to the good manufacturing practice requirements set forth in parts 210, 211, 600, 606, and 820 of this chapter.

(b) *Availability of product.* No biologics license shall be issued unless:

(1) The product intended for introduction into interstate commerce is available for examination, and

(2) Such product is available for inspection during all phases of manufacture.

(c) *Manufacturing process—impairment of assurances.* No product shall be licensed if any part of the process of or relating to the manufacture of such product, in the judgment of the Director, Center for Biologics Evaluation and Research, would impair the assurances of continued safety, purity, and potency as provided by the regulations contained in this chapter.

(d) *Inspection—compliance with requirements.* A biologics license shall be issued or a biologics license application approved only after inspection of the establishment(s) listed in the biologics license application and upon a determination that the establishment(s) complies with the standards established in the biologics license application and the requirements prescribed in applicable regulations.

(e) *One biologics license to cover all locations.* One biologics license shall be issued to cover all locations meeting the establishment standards identified in the approved biologics license application and each location shall be subject to inspection by FDA officials.

35. Section 601.21 is revised to read as follows:

§ 601.21 Products under development.

A biological product undergoing development, but not yet ready for a biologics license, may be shipped or otherwise delivered from one State or possession into another State or possession provided such shipment or delivery is not for sale, barter, or exchange, except as provided in section 505(i) of the Federal Food, Drug, and Cosmetic Act, as amended, and the regulations thereunder (21 CFR parts 312 and 812).

36. Section 601.22 is amended by revising the section heading and the first and second sentences to read as follows:

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

A biologics license issued to a manufacturer and covering all locations of manufacture shall authorize persons other than such manufacturer to conduct at places other than such locations the initial, and partial manufacturing of a product for shipment solely to such manufacturer only to the extent that the names of such persons and places are registered with the Commissioner of Food and Drugs and either of the following is found upon application of such manufacturer, that the product is in short supply due either to the peculiar growth requirements of the organism involved or to the scarcity of the animal required for manufacturing purposes, and such manufacturer has established with respect to such persons and places such procedures, inspections, tests or other arrangements as will assure full compliance with the applicable regulations of this subchapter related to continued safety, purity, and potency. Such persons and places shall be subject to all regulations of this subchapter except §§ 601.2 to 601.6, 601.9, 601.10, 601.20, 601.21 to 601.33, and §§ 610.60 to 610.65 of this chapter. * * *

37. Sections 601.25 is amended in paragraph (b)(3) under ''Biological Products Review Information'' by revising section VIII and by revising the third sentence of paragraph (f)(3) to read as follows:

§ 601.25 Review procedures to determine that licensed biological products are safe, effective, and not misbranded under prescribed, recommended, or suggested conditions of use.

* * * * *

(b) * * *

(3) * * *

BIOLOGICAL PRODUCTS REVIEW INFORMATION

* * * * *

VIII. If the submission is by a licensed manufacturer, a statement signed by the authorized official of the licensed manufacturer shall be included, stating that to the best of his or her knowledge and belief, it includes all information, favorable and unfavorable, pertinent to an evaluation of the safety, effectiveness, and labeling of the product, including information derived from investigation, commercial marketing, or published literature. If the submission is by an interested person other than a licensed manufacturer, a statement signed by the person responsible for such submission shall be included, stating that to the best of his knowledge and belief, it fairly reflects a balance of all the available information, favorable and unfavorable available to him, pertinent to an evaluation of the safety, effectiveness, and labeling of the product.

* * * * *

(f) * * *

(3) * * * Where the Commissioner determines that the potential benefits outweigh the potential risks, the proposed order shall provide that the biologics license for any biological product, falling within this paragraph will not be revoked but will remain in effect on an interim basis while the data necessary to support its continued marketing are being obtained for evaluation by the Food and Drug Administration. * * *

* * * * *

38. Section 601.26 is amended by revising the second sentence of the introductory text of paragraph (e), the first, fourth and fifth sentences of paragraph (f)(1), the second sentence of paragraph (f)(2), and the first sentence of paragraph (f)(3) to read as follows:

§ 601.26 Reclassification procedures to determine that licensed biological products are safe, effective, and not misbranded under prescribed, recommended, or suggested conditions of use.

* * * * *

(e) * * * Where the Commissioner determines that there is a compelling medical need and no suitable alternative therapeutic, prophylactic, or diagnostic agent for any biological product that is available in sufficient quantities to meet current medical needs, the final order shall provide that the biologics license application for that biological product will not be revoked, but will remain in effect on an interim basis while the data

necessary to support its continued marketing are being obtained for evaluation by the Food and Drug Administration. * * *

(f) *Additional studies and labeling.* (1) Within 60 days following publication of the final order, each licensed manufacturer for a biological product designated as requiring further study to justify continued marketing on an interim basis, under paragraph (e) of this section, shall submit to the Commissioner a written statement intended to show that studies adequate and appropriate to resolve the questions raised about the product have been undertaken. * * * The Commissioner may extend this 60-day period if necessary, either to review and act on proposed protocols or upon indication from the licensed manufacturer that the studies will commence at a specified reasonable time. If no such commitment is made, or adequate and appropriate studies are not undertaken, the biologics license or licenses shall be revoked. * * *

(2) * * * If the progress report is inadequate or if the Commissioner concludes that the studies are not being pursued promptly and diligently, or if interim results indicate the product is not a medical necessity, the biologics license or licenses shall be revoked.

(3) Promptly upon completion of the studies undertaken on the product, the Commissioner will review all available data and will either retain or revoke the biologics license or licenses involved. * * *

* * * * *

39. Section 601.51 is amended by revising the section heading, the first sentence of paragraph (a), and paragraph (b) to read as follows:

§ 601.51 Confidentiality of data and information in applications for biologics licenses.

(a) For purposes of this section the biological product file includes all data and information submitted with or incorporated by reference in any application for a biologics license, IND's incorporated into any such application, master files, and other related submissions. * * *

(b) The existence of a biological product file will not be disclosed by the Food and Drug Administration before a biologics license application has been approved unless it has previously been publicly disclosed or acknowledged. The Director of the Center for Biologics Evaluation and Research will maintain a list available for public disclosure of biological products for which a license application has been approved.

* * * * *

PART 607—ESTABLISHMENT REGISTRATION AND PRODUCT LISTING FOR MANUFACTURERS OF HUMAN BLOOD AND BLOOD PRODUCTS

40. The authority citation for 21 CFR part 607 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 355, 360, 371, 374; 42 U.S.C. 216, 262.

41. Section 607.20 is amended by revising paragraph (b) to read as follows:

§ 607.20 Who must register and submit a blood product list.

* * * * *

(b) Preparatory to engaging in the manufacture of blood products, owners or operators of establishments who are submitting a biologics license application to manufacture blood products are required to register before the biologics license application is approved.

* * * * *

42. Section 607.21 is amended by revising the second sentence to read as follows:

§ 607.21 Times for establishment registration and blood product listing.

* * * If the owner or operator of the establishment has not previously entered into such operation (defined in § 607.3(d)) for which a license is required, registration shall follow within 5 days after the submission of a biologics license application in order to manufacture blood products. * * *

PART 610—GENERAL BIOLOGICAL PRODUCTS STANDARDS

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

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371; 42 U.S.C. 216, 262, 263, 263a, 264.

44. Section 610.13 is amended by revising the introductory paragraph and the first sentence of paragraph (a)(1) to read as follows:

§ 610.13 Purity.

Products shall be free of extraneous material except that which is unavoidable in the manufacturing process described in the approved biologics license application. In addition, products shall be tested as provided in paragraphs (a) and (b) of this section.

(a)(1) *Test for residual moisture.* Each lot of dried product shall be tested for residual moisture and shall meet and not exceed established limits as specified by an approved method on file in the biologics license application. * * *

* * * * *

45. Section 610.53 is amended by revising paragraph (d) to read as follows:

§ 610.53 Dating periods for licensed biological products.

* * * * *

(d) *Exemptions.* Exemptions or modifications shall be made only upon written approval, in the form of a supplement to the biologics license application, issued by the Director, Center for Biologics Evaluation and Research.

46. Section 610.63 is revised to read as follows:

§ 610.63 Divided manufacturing responsibility to be shown.

If two or more licensed manufacturers participate in the manufacture of a biological product, the name, address, and license number of each must appear on the package label, and on the label of the container if capable of bearing a full label.

PART 640—ADDITIONAL STANDARDS FOR HUMAN BLOOD AND BLOOD PRODUCTS

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

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371; 42 U.S.C. 216, 262, 263, 263a, 264.

48. Section 640.6 is amended by revising the introductory text to read as follows:

§ 640.6 Modifications of Whole Blood.

Upon approval by the Director, Center for Biologics Evaluation and Research, of a supplement to the biologics license application for Whole Blood a manufacturer may prepare Whole Blood from which the antihemophilic factor has been removed, provided the Whole Blood meets the applicable requirements of this subchapter and the following conditions are met:

* * * * *

49. Section 640.21 is amended by revising paragraph (c) to read as follows:

§ 640.21 Suitability of donors.

* * * * *

(c) Plateletpheresis donors shall meet criteria for suitability as described in a biologics license application or a supplement to the biologics license application, and must have the written approval of the Director, Center for Biologics Evaluation and Research, Food and Drug Administration.

50. Section 640.22 is amended by revising paragraph (c) to read as follows:

§ 640.22 Collection of source material.

* * * * *

(c) If plateletpheresis is used, the procedure for collection shall be as described in a biologics license application or a supplement to a biologics license application, and must have the written approval of the Director, Center for Biologics Evaluation and Research, Food and Drug Administration.

* * * * *

51. Section 640.64 is amended by revising the second sentence of the introductory text of paragraph (c) to read as follows:

§ 640.64 Collection of blood for Source Plasma.

* * * * *

(c) * * * One of the following formulas shall be used in the indicated volumes, except that a different formula may be used for plasma for manufacture into noninjectable products if prior written approval is obtained from the Director of the Center for Biologics Evaluation and Research at the time of licensing or in the form of a supplement to the biologics license application for Source Plasma.

* * * * *

52. Section 640.65 is amended by revising the last sentence of paragraph (a) to read as follows:

§ 640.65 Plasmapheresis.

(a) * * * This procedure shall be described in detail in the biologics license application.

* * * * *

53. Section 640.71 is amended by revising the introductory text of paragraphs (a) and (b) and by revising paragraph (b)(1) to read as follows:

§ 640.71 Manufacturing responsibility.

(a) All steps in the manufacture of Source Plasma, including donor examination, blood collection, plasmapheresis, laboratory testing, labeling, storage, and issuing shall be performed by personnel of the licensed manufacturer of the Source Plasma, except that the following tests may be performed by personnel of a manufacturer licensed for blood or blood derivatives under section 351(a) of the Public Health Service Act, or by a clinical laboratory that meets the standards of the Clinical Laboratories Improvement Act of 1967 (CLIA) (42 U.S.C. 263a): *Provided*, The establishment or the clinical laboratory is qualified to perform the assigned test(s).

* * * * *

(b) Such testing shall not be considered divided manufacturing, which requires two biologics licenses for Source Plasma: *Provided*, That

(1) The results of such tests are maintained by the licensed manufacturer of the Source Plasma whereby such results may be reviewed by a licensed physician as required in § 640.65(b)(2) and by an authorized representative of the Food and Drug Administration.

* * * * *

54. Section 640.74 is amended by revising paragraph (a) and the last sentence of paragraph (b)(2) to read as follows:

§ 640.74 Modification of Source Plasma.

(a) Upon approval by the Director, Center for Biologics Evaluation and Research, Food and Drug Administration, of a supplement to the biologics license application for Source Plasma, a manufacturer may prepare Source Plasma as a liquid product for a licensed blood derivative manufacturer who has indicated a need for a liquid product.

(b) * * *

(2) * * * Such evidence may be submitted by either the licensed manufacturer of the Source Plasma Liquid or the manufacturer of the final blood derivative product who has requested the Source Plasma Liquid.

* * * * *

PART 660—ADDITIONAL STANDARDS FOR DIAGNOSTIC SUBSTANCES FOR LABORATORY TESTS

55. The authority citation for 21 CFR part 660 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371; 42 U.S.C. 216, 262, 263, 263a, 264.

56. Section 660.21 is amended by revising paragraphs (a)(3) and (d) to read as follows:

§ 660.21 Processing.

(a) * * *

(3) A lot may be subdivided into clean, sterile vessels. Each subdivision shall constitute a sublot. If lots are to be subdivided, the manufacturer shall include this information in the biologics license application. The manufacturer shall describe the test specifications to verify that each sublot is identical to other sublots of the lot.

* * * * *

(d) *Volume of final product.* Each manufacturer shall identify the possible final container volumes in the biologics license application.

* * * * *

57. Section 660.30 is amended by revising paragraph (b) to read as follows:

§ 660.30 Reagent Red Blood Cells.

* * * * *

(b) *Source.* Reagent Red Blood Cells shall be prepared from human peripheral blood meeting the criteria of §§ 660.31 and 660.32, or from umbilical cord cells which shall be collected and prepared according to the manufacturer's biologics license application.

58. Section 660.33 is amended by revising the fifth sentence to read as follows:

§ 660.33 Testing of source material.

* * * Where fewer than three donor sources of an antibody specificity are available, test discrepancies shall be resolved in accordance with the manufacturer's biologics license application. * * *

Dated: July 22, 1998.

Michael A. Friedman,

Acting Commissioner of Food and Drugs.

Donna E. Shalala,

Secretary of Health and Human Services.

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DEPARTMENT OF THE INTERIOR

Office of Surface Mining Reclamation and Enforcement

30 CFR Parts 707 and 874

RIN 1029–AB89

Abandoned Mine Land (AML) Reclamation Program; Enhancing AML Reclamation

AGENCY: Office of Surface Mining Reclamation and Enforcement, Interior.

ACTION: Proposed rule, reopening and extension of comment period.

SUMMARY: The Office of Surface Mining Reclamation and Enforcement (OSM) is reopening and extending the comment period for the proposed rule, Enhancing AML Reclamation, published on June 25, 1998 (63 FR 34768). The comment period closed on July 27, 1998, and is being reopened and extended for 15 days.

DATES: *Written comments:* We will accept written comments on the proposed rule until 5 p.m., Eastern time, on August 11, 1998.

ADDRESSES: If you wish to comment, you may mail or hand deliver comments