adding, in their place, the words ''taxes, and interest'';

b. The introductory text of paragraph (b) is amended by removing the words ''and taxes'' wherever they appear and adding, in their place, the words ''taxes, and interest'';

c. Paragraph (c) is amended by removing the words ''and taxes assessed in the liquidation'' and adding, in their place, the words ''taxes, and interest assessed in the liquidation'' and by removing the words ''and taxes assessed in the reliquidation'' and adding, in their place, the words ''taxes, and interest assessed in the reliquidation''; and

d. In paragraph (d), the paragraph heading and the paragraph text are amended by adding ''and interest'' after ''taxes''.

PART 174—PROTESTS

1. The authority citation for Part 174 continues to read as follows:

Authority: 19 U.S.C. 66, 1514, 1515, 1624.

§ 174.11 [Amended]

2. In § 174.11, paragraph (c) is amended by adding '', including the accrual of interest,'' after ''character''.

§ 174.12 [Amended]

3. In § 174.12, paragraph (a)(2) is amended by adding '', or receiving a refund of,'' after ''paying'.

Approved: July 28, 1999.

Raymond W. Kelly,

Commissioner of Customs.

Dennis M. O'Connell,

Acting Deputy Assistant Secretary of the Treasury.

[FR Doc. 99–26882 Filed 10–19–99; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 3, 5, 10, 20, 50, 56, 58, 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 Service Act; Implementation of Biologics License; Elimination of Establishment License and Product License

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the biologics regulations to eliminate references to establishment licenses and product licenses for all products regulated under the Public Health Service Act (the 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 will file a single biologics license application (BLA) with the agency. Upon approval of the BLA, a manufacturer will 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 implements certain sections of the FDA Modernization Act of 1997 (FDAMA).

DATES: *Effective date*: The regulation is effective December 20, 1999.

Compliance Date: Submit all applications with the Form FDA 356h by December 20, 1999, and submit any application for licensure as a BLA by October 20, 2000.

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

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of July 31, 1998 (63 FR 40858), FDA proposed to amend the biologics and other drug regulations to eliminate references to the PLA and ELA and to replace such references with the BLA. FDA provided 75 days for comments on the proposed rule. FDA held a public meeting, announced in the **Federal Register** of August 11, 1998 (63 FR 42773), on September 2, 1998, to discuss the BLA/biologics license scheme. FDA also invited the submission of written comments to the docket at the public meeting. The transcript of the public meeting and written comments to the proposed rule are on file in the Dockets Management Branch (HFA–305), 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Prior to the issuance of the proposed rule, FDA had already reviewed its process of licensing biological products and had 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. 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 the following specified biotechnology and synthetic biological products licensed under section 351 of the PHS Act (42 U.S.C. 262 *et seq.*): (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. That provision applied only to those products that FDA determined under 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 received 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 Form FDA 356h entitled ''Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use.'' Form FDA 356h was revised as a ''Reinventing Government'' initiative to harmonize application procedures between CBER and the Center for Drug Evaluation and Research (CDER) as outlined in the President's November 1995 National Performance Review Report entitled ''Reinventing the Regulation of Drugs Made From Biotechnology.'' In the notice, FDA advised that applicants for biologics licenses for products specified in § 601.2(c) as well as autologous somatic cell therapy products could begin to use Form FDA 356h immediately and were required to do so beginning January 8, 1998. FDA advised applicants for licenses for other biological products that the agency would announce in the future when they can voluntarily begin to use and will be required to use Form FDA 356h. Upon approval of a BLA submitted on Form FDA 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. As a consequence of this final

rule, all manufacturers requesting approval to introduce, or deliver for introduction, a biological product into interstate commerce must use Form FDA 356h to submit a BLA in lieu of separate establishment and product applications.

On November 21, 1997, the President signed into law FDAMA (Pub. L. 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 (the Secretary) (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.

With the consolidation of the ELA's and PLA's into a single BLA, the amount of information formerly included in the ELA will be reduced, but not eliminated. Much of the information previously reviewed in an ELA at FDA will be reviewed by FDA investigators at the manufacturing site during a preapproval inspection. Some information formerly included in the ELA will now be submitted as ''chemistry, manufacturing, and controls'' (CMC) information or under the ''establishment description'' section of Form FDA 356h. The type and amount of information related to the establishment will 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 has prepared a series of guidance documents. The following guidance documents are available: (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'' (issued on the internet, November 1994); (4) ''Guidance for Industry: Content and Format of Chemistry, Manufacturing and Controls and Establishment Description Information for a Vaccine or Related Product'' (64 FR 518, January 5, 1999); (5) ''Guidance for Industry for the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Plasma-Derived Biological Products, Animal Plasma, or Serum-Derived Products'' (64 FR 7896, February 17, 1999); (6) ''Guidance for Industry: Content and Format of Chemistry, Manufacturing and Controls, and Establishment Description Information for a Biological In Vitro Diagnostic Product'' (64 FR 11023, March 8, 1999); (7) ''Guidance for Industry: On the Content and Format of Chemistry, Manufacturing and Controls, and Establishment Description Information for an Allergenic Extract or Allergen Patch Test'' (64 FR 20006, April 23, 1999); and (8) ''Guidance for Industry: For the Submission of Chemistry, Manufacturing and Controls, and Establishment Description Information for Human Blood and Blood Components Intended for Transfusion or for Further Manufacture and for the Completion of the Form FDA 356h Application to Market a New Drug, Biologic or an Antibiotic Drug for Human Use'' (64 FR 25049, May 10, 1999). All of these guidance documents can be downloaded from the CBER Guidelines/Guidance document World Wide Web page at ''http://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, 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.

II. Highlights of Proposed Rule

A. Introduction

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

In the proposed rule of July 31, 1998, FDA proposed changes to the regulations intended to implement use of the BLA and to implement FDAMA. The proposed rule would also change certain definitions to be more consistent with FDAMA and eliminate references to the PLA and ELA. In the following sections of this document, FDA outlines in greater detail the provisions of the proposed rule.

B. Definitions 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 proposed to amend the definition of ''establishment'' in § 600.3(w) (21 CFR 600.3(w)) to clarify that the term has the same meaning as ''facility'' in section 351 of the PHS Act. FDA also proposed to amend the definition of ''standards'' in § 600.3(n) to indicate that the term refers to specifications and procedures established in BLA's designed to ensure the continued safety, purity, and potency of biological products as well as adherence to specifications and procedures in applicable regulations. 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) also would reduce confusion in the biologics regulations by establishing consistency with FDA's current regulation at 21 CFR 601.5(b)(4) regarding the revocation of licenses. FDA proposed to delete the term ''licensee'' as used in the biologics regulations in order to reduce confusion and to make clear 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.''

C. Elimination of PLA/ELA and Implementation of BLA

FDA proposed that the terms ''biologics license'' or ''biologics license application'' be substituted in lieu of references to PLA's and ELA's and product and establishment licenses in all regulations in 21 CFR chapter I. In a few instances, references to product and establishment licenses would be retained for historical accuracy, e.g., § 601.25 (21 CFR 601.25) and 21 CFR 601.26.

Under the proposed rule, 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 Form FDA 356h. Manufacturers would no longer be required to submit product or establishment information on one of the many different PLA and ELA forms formerly in use. Upon approval of the BLA, FDA would issue an approval letter that in general terms states that FDA 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.

Under proposed § 601.2(a), manufacturers would list in the BLA the addresses of all locations of manufacture of a biological product. FDA believes this will 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.

Under proposed § 601.9(c), for manufacturers of some biological products that would be able to list multiple products in a single BLA, (such as blood and blood components and nonstandardized allergenic products) and for which FDA will issue a single biologics license to the manufacturer for more than one product, FDA would be able to license compliant locations and products and exclude noncompliant locations.

D. Radioactive Biological Products

FDA proposed 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. The regulation would clarify when a manufacturer of a radioactive biological product should submit a new drug application (NDA) to CDER or a BLA to CBER. The regulation provides that when the biological component of a radioactive coupled antibody determines the site of action, normally a BLA would be submitted. The regulation will provide sufficient flexibility to take into account situations that may arise in the future where the scientific issues associated with a 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'' of October 31, 1991. The proposed changes should not be construed as an attempt to address or implement the requirements of section 122 of FDAMA, ''Requirements for Radiopharmaceuticals.''

FDA is also amending § 310.4 (21 CFR 310.4) to make it consistent with § 601.2(b). Revisions to the proposed changes to § 310.4 have been made for clarity. Certain changes to both § 310.4(a) and (b) are necessary in order to make congruous the regulations that describe whether CBER or CDER will have primary jurisdiction over a radioactive biological product. The amendment to § 310.4(b) is prospective and does not alter the approval mechanism of any currently approved radioactive biological products that have approved NDA's or approved establishment and product licenses. Section 310.4(a) is amended to make it consistent with § 601.2(b) and to clarify that if any biological product has an approved license under section 351 of the PHS Act, it is not required to have an approved application under section 505 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355).

E. Current Good Manufacturing Practice Requirements

FDA discussed in the preamble to the proposed rule the applicability of current good manufacturing practices (CGMP) requirements for biological products. For clarity FDA proposed in § 601.2(d) that the CGMP requirements in parts 210, 211, 600, 606, and 820 (21 CFR parts 210, 211, 600, 606, and 820) are included, as applicable, as part of the establishment requirements for the production of a biological product.

III. Comments on the Proposed Rule and FDA Responses

FDA received two letters of comment in response to the proposed rule; one letter from an organization representing the blood and blood component industry and another from a manufacturer of biological products. Comments received and FDA's responses to the comments are discussed below. There were also a few technical changes, to be consistent with other changes in this rulemaking or to be consistent with statutory language in FDAMA, made to the following regulations: 21 CFR 50.3(b)(12), 56.102(b)(11), 58.3(e)(13); §§ 600.81, 601.2, and 601.21 (21 CFR 601.21). FDA is also revising 21 CFR 601.22 to remove wording that was inadvertently added to the regulation in the proposed rule that implied that either of two requirements must be met. The change eliminates this ambiguity and reinstates the original intent that both requirements must be met.

1. A comment was supportive of the concept of a BLA and use of the Form FDA 356h but strongly urged FDA to ensure that the intended paperwork reduction and efficiency goals are achieved. The comment stated that the simplification of the BLA will be affected by how supplemental applications are handled and expressed concern that this be adequately addressed. The comment specifically requested that in implementing the BLA for blood and blood components that one supplement to the BLA be acceptable to report a change in the manufacturing of Platelets, Pheresis for all manufacturing locations.

FDA agrees that it is important to implement the rule in a manner that will reduce unnecessary burdens; accordingly the agency is implementing several mechanisms for ensuring that this is the case. Manufacturers of some biological products will be able to list multiple products in a BLA and FDA will issue a single biologics license to the manufacturer for more than one product. FDA intends to use this approach generally with products that both have been on the market for a long period of time and that FDA has considerable knowledge and expertise regulating. Currently, only products such as blood and blood components and nonstandardized allergenic products will be handled in a single BLA. Therefore, a manufacturer of blood and blood components will 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, and

Cryoprecipitated AHF). FDA believes this consolidation of forms and submissions will 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.

With regard to manufacturing changes, the BLA system will 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 the final rule, 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, i.e., a separate supplement for each blood component manufactured at each location. Under the final rule, the manufacturer would only be required to submit one supplement to the BLA describing the change for all of the products and locations involved. Of course, all data (including applicable validation and quality control testing) and information related to all the affected products and locations would be expected to be present in the supplement. Section 123 of FDAMA states, in part, that the Secretary shall approve a BLA 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. FDA intends to ensure that the final rule will be properly implemented and is providing adequate training and management oversight to ensure that this happens.

2. One comment requested the elimination of the use of the Form FDA 2567, Transmittal of Labels and Circulars, as being duplicative of Form FDA 356h.

FDA disagrees that the form is duplicative. FDA Form 2567 is used for any submission of labeling, including promotional labeling. This form (OMB Control No. 0910–0039) contains information that is not requested in the Form FDA 356h, which is necessary for the adequate tracking of labeling submissions to FDA. It provides specific identification of the labeling changes, including revision number and the type of labeling and provides a check list for the type of changes that have been made to the labeling. The form provides a clear, simple method for transmitting comments on the labeling to and from the manufacturers allowing for quick return of comments and easy identification of sequential revisions.

3. One comment stated that the ''Draft Guidance for Industry: For the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Blood and Blood Components Intended for Transfusion or for Further Manufacture and For the Completion of the Form FDA 356h, 'Application to Market a New Drug, Biologic or an Antibiotic Drug for Human Use''' (63 FR 37401, July 10, 1998) requires, for the first time, submission of information regarding certain manufacturing standard operating procedures (SOP's), contracts, organizational characteristics, organization diagrams, physical plant, major equipment, and quality assurance.

FDA disagrees in part with this comment. Guidance documents do not set forth requirements; they provide the agency's current thinking on a topic and are nonbinding. A review of SOP's, physical plant information, and information on contracts have always been part of an assessment of a product's safety, purity, and potency. FDA has the authority to require sponsors to submit such information in license applications under section 351 of the PHS Act and 21 CFR part 601. In the more recent past, FDA has found that inadequate organizational/managerial oversight and quality assurance problems at firms have resulted in firms being out of compliance with the regulations applicable to blood and blood components and have been the cause of problems leading to significant enforcement action by the agency. FDA believes it is important to review information related to the managerial/organizational oversight and quality assurance in order to ensure that a firm can manufacture products that meet the applicable regulatory and statutory requirements. Therefore, FDA will review such information as part of the BLA. FDA believes that the burden associated with the submission of such information will be minimal. Describing organizational aspects can be done through the use of organizational charts, and under CGMP regulations, quality assurance is already a requirement. The submission of descriptions of such organizations should require minimal time for gathering and preparing the information. In addition, since other information previously reviewed as part of the PLA and ELA will not be required to be included in a BLA, FDA estimates that the net effect is no increase in burden or a slightly lower burden. For example, information that will no longer be submitted in a BLA but should, as appropriate, be available for an establishment inspection includes, but is not limited, to such information as: (1) Floor plans of facilities, auxiliary facilities and self-contained mobile units to show locations of major equipment, hand washing facilities and restrooms; (2) Heating, ventilation, and air conditioning information; (3) curriculum vitae for physicians, physician substitutes, authorized officials and their alternates, and managers; (4) ''statement of understanding'' from physicians and authorized officials; (5) proof of state licensure of physicians; (6) physician substitute certification of training and cardiopulmonary resuscitation; (7) supervisor qualifications and number of people supervised in the areas of donor suitability, blood collection, laboratory processing, and testing; (8) description of any other uses for the area where blood collection or processing occurs; (9) description of provisions for housekeeping, pest control, and lighting; (10) description of records maintenance method, including when they are made, how long they are stored, and how they are maintained to permit effective recall; and (11) copy of the certificate of incorporation. FDA is currently reviewing comments on the draft CMC guidance and will consider the comments in any revision made to the ''Draft Guidance for Industry: For the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Blood and Blood Components Intended for Transfusion or for Further Manufacture and for the Completion of the Form FDA 356h, 'Application to Market a New Drug, Biologic or an Antibiotic Drug for Human Use.'''

4. One comment supported the proposed revision to § 601.21 but recommended that the regulation reference the appropriate section of the act applicable to investigational device exemptions.

FDA agrees with the comment and is amending § 601.21 in the final rule to reference section 520(g) of the act (21 U.S.C. 360j(g)) that provides for exemption of devices for investigational use.

FDA has considered all comments received in response to the proposed rule and has determined that the proposed rule should be issued as a final rule. Accordingly, FDA is issuing as a final rule changes to the biologics regulations that provide for the use of a ''biologics license application'' and ''biologics license'' for the licensure of all products under section 351 of the PHS Act.

IV. Effective Dates and Other Implementation Issues

FDA is providing a 10-month transition period for implementation of the BLA. FDA recognizes that it may take applicants time to switch format from PLA's and ELA's to BLA's. Any PLA and ELA for a biological product pending on the effective date of these regulations will be reviewed as submitted. Notwithstanding the new regulations, new submissions by the manufacturer will not be necessary for these products. FDA will continue to accept PLA's and ELA's in lieu of a BLA until October 20, 2000, of this final rule. However, all applications submitted to the agency after the effective date of the final rule will be required to include all information indicated in Form FDA 356h in order for the application to be considered as complete. PLA's and ELA's received after the effective date of the final rule will be administratively handled by FDA as a BLA. If the PLA and ELA are sufficient for licensure, FDA will issue a biologics license. 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.

Under new § 601.2(e), a manufacturer already holding an approved ELA and PLA for a biological product will 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, will be deemed to constitute a BLA under section 351 of the PHS Act .

V. Analysis of Impacts

A. Reduction in Burden

The use of the harmonized Form FDA 356h for all biological products and drugs regulated by CBER and CDER will 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 will no longer have to prepare a PLA and an ELA to submit to the agency for approval. The amount of information that manufacturers will need to provide in a BLA will be less than that previously required in a PLA and ELA. These changes will enable manufacturers to devote fewer resources to submitting documentation to the agency. Much of the information previously reviewed in an ELA at FDA will be reviewed by FDA investigators 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 added substantially to the cost of licensing the product.

The inclusion of reference to parts 210, 211, 600, 606, and 820 in the final rule as establishment requirements only serve to clarify existing requirements and will not impose any additional burden on industry. Biological products regulated under section 351 of the PHS Act, are already subject to the CGMP's in parts 600, 606 and, as applicable, parts 210 and 211, or 820.

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

FDA has examined the impact of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (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 rule is consistent with the regulatory philosophy and principles identified in Executive Order 12866. In addition, the 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 rule will be a substantial reduction in burdens on a manufacturer filing an application to market a biological product. In addition, FDA anticipates that the rule will 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 rule will be a substantial reduction in reporting burdens, the agency certifies that the 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 final rule contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501–3520). The title, description, and the respondent description of the information collection provisions are shown below with an estimate of the annual reporting burden. Included in the estimate is the time for reviewing the instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

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: This final rule revises the regulations regarding the procedures for application for approval to market a biological product regulated under section 351 of the PHS Act. Under the regulations, a manufacturer will submit to FDA the appropriate establishment and product information in a single BLA in lieu of filing a separate ELA and PLA. 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 final 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 final rule will 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 average paperwork burden for manufacturers filing one application that consolidates the information currently required under both the PLA and ELA will decrease 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 (FY) 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 in the final rule that relate to certain information to be included in a license application including § 640.21(c) (21 CFR 640.21(c)), § 640.22(c) (21 CFR 640.22(c)), 21 CFR 640.65(a), and 660.21(a)(3) and (d). The burden associated with the information collection requirements in these regulations is included in the following reporting burden estimate for § 601.2.

The regulation also makes several technical amendments to conform the language throughout the biological product regulations to the changes made final here for § 601.2. Specifically, the final 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;'' and ''licensee'' is replaced with ''licensed manufacturer.'' These technical changes do not have an impact on either the substantive requirements or the paperwork burden of these requirements, each of which carry OMB clearance numbers as follows: 21 CFR 207.20(c) and 207.21(a) (0910–0045); §§ 600.80(c)(2) and 600.81 (0910–0308); § 601.25(b)(3) (0910–0039); 21 CFR 607.20(b) and 607.21 (0910–0052); and 21 CFR 610.63 and 640.71(b)(1) (0910–0116).

The following regulations relate to the submission of additional information in certain supplements to a BLA. Regulations in 21 CFR 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 regulation in FY 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 of this document. Section 640.6 (21 CFR 640.6) requires that an applicant submit a request to make a certain modification of Whole Blood. The number of supplements relating to Whole Blood filed by an applicant in FY 1997 totaled 74. Because the agency could not easily 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, regardless of whether the supplement was filed specific to § 640.6.

The remaining regulations, §§ 640.21(c), 640.22(c), 21 CFR 640.64(c), and 640.74(a) and (b)(2), refer to information that is collected under § 601.12, (OMB Control No. 0910–0315) under which the collection of information burden is calculated. Moreover, the final rule makes only technical changes to these regulations. For example, the term ''product license'' is changed to ''biologics license,'' and the term ''product licensee'' is changed to ''licensed manufacturer.''

As required by section 3506(c)(2)(B) of the PRA, FDA provided an opportunity for public comment on the information collection provisions of the proposed rule (63 FR 40858). One letter of comment on the information collection provisions was submitted to OMB. Most of the comments submitted to OMB were the same as those submitted directly to FDA in response to the proposed rule. FDA's responses to these comments are found above in section III of this document. Responses to additional comments in the letter received by OMB that were not addressed previously are addressed in the following paragraphs.

1. A comment pointed out that few new BLA's for blood and blood components will be submitted to the agency. More frequently changes to already approved applications are submitted as supplements. These supplements will now use Form FDA 356h for submission to the agency. The comment stated if Form FDA 356h is merely substituted for the current forms and manufacturers must continue to file a supplement for each product at each location, the paperwork will actually increase because of the increased CMC and establishment requirements.

FDA agrees that few new BLA's for blood and blood components are submitted to the agency. However, FDA disagrees that the burden will increase. Previously, manufacturers desiring to make a single manufacturing change that would affect multiple products were required to submit a supplement to each individual product and establishment application. Under this final rule 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. Therefore, fewer supplements should be submitted by applicants. The size of the decrease in supplements will depend on how the applicant bundles the submissions. At the time of submission of a supplement, FDA expects that all data and information pertinent to the supplement be present or the FDA may refuse to file the application (see the guidance entitled ''Center for Biologics Evaluation and Research (CBER): Refusal to File (RTF) Guidance for Product License Applications (PLA's) and Establishment License Applications (ELA's)'' (58 FR 38770, July 20, 1993)). Therefore, if an applicant wishes to submit a change affecting multiple locations in one supplement, and all data and information supporting the change at those locations are present in the supplement, FDA will accept such a submission. FDA, therefore, estimates that there will be an overall reduction in burden associated with this final rule.

2. Another comment stated that the number of respondents and supplement submissions, and the hours per submission were severely underestimated by FDA. The comment expressed concern that FDA was unable to specifically enumerate the number of submissions made under § 640.6 and suggested that this was ''indicative of a larger problem.'' The comment described FDA's approach to burden estimates as disturbing for other reasons such as not addressing supplements for products other than Whole Blood, and because the agency's internal tracking, accounting, and documentation systems may be inadequate. The comment stated that FDA had trouble distinguishing between supplemental license applications submitted under §§ 640.6 and 601.12. For the purposes of burden hour development, the distinction between supplements submitted under § 640.6 and those under § 601.12 is somewhat artificial because the burden for the regulated community to prepare the supplement is identical regardless of the section under which such information is submitted.

The comment has misinterpreted the estimate. In preparing this burden estimate, FDA estimated the burden for those sections of the regulations being amended, including § 640.6. No changes in § 601.12 were included in this rulemaking, therefore FDA has not estimated the burden of this section which already has an approved OMB control number (0910–0315). The burden associated with the preparation of supplemental applications is also

included in the estimate for § 601.12 and is outside the scope of this rule. Since § 640.6 applies specifically to Whole Blood, an estimate as seen in Table 1 of this document is limited to only Whole Blood submissions and the associated reporting burden hours. The number of respondents reflects the number of FY 1997 supplements submitted specifically for Whole Blood, and the 8 hours is an accurate estimate for this type of submission. For purposes of carrying out its obligations for the review of applications, FDA continues to believe that it is unnecessary to keep separate track of those applications submitted under § 640.6, because review of these supplemental applications is not different from other supplemental applications submitted under § 601.12. Because FDA's current tracking system does not allow a search of the data base that would identify accurately the number of Whole Blood supplements submitted under § 640.6, FDA looked at the number of all supplements related only to Whole Blood, which is the scope of this regulation, and conservatively estimated the burden to account for more rather than fewer burden hours. Therefore, the estimated burden hours are likely to be higher than those that may actually occur.

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.

The information collection provisions of the final rule have been submitted to OMB for review. Prior to the effective date of the final rule, FDA will publish a document in the **Federal Register** announcing OMB's decision to approve, modify, or disapprove the information collection provisions in the final rule. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

D. Environmental Impact

The agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

List of Subjects

21 CFR Part 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 50

Human research subjects, Prisoners, Reporting and recordkeeping requirements, Safety.

21 CFR Part 56

Human research subjects, Reporting and recordkeeping requirements, Safety.

21 CFR Part 58

Laboratories, Reporting and recordkeeping requirements.

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, 21 CFR parts 3, 5, 10, 20, 50, 56, 58, 207, 310, 312, 316, 600, 601, 607, 610, 640, and 660 are amended 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, 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, 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), 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 continues 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 continues 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 50—PROTECTION OF HUMAN SUBJECTS

10. The authority citation for 21 CFR part 50 continues to read as follows:

Authority: 21 U.S.C. 321, 346, 346a, 348, 352, 353, 355, 360, 360c–360f, 360h–360j, 371, 379e; 42 U.S.C. 216, 241, 262, 263b–263n.

11. Section 50.3 is amended by revising paragraph (b)(12) to read as follows:

§ 50.3 Definitions.

* * * * *

(b) * * *

(12) An application for a biologics license, described in part 601 of this chapter.

* * * * *

PART 56—INSTITUTIONAL REVIEW BOARDS

12. The authority citation for 21 CFR part 56 continues to read as follows:

Authority: 21 U.S.C. 321, 346, 346a, 348, 351, 352, 353, 355, 360, 360c–360f, 360h–360j, 371, 379e, 381; 42 U.S.C. 216, 241, 262, 263b–263n.

13. Section 56.102 is amended by revising paragraph (b)(11) to read as follows:

§ 56.102 Definitions.

* * * * *

(b) * * *

(11) An application for a biologics license, described in part 601 of this chapter.

* * * * *

PART 58—GOOD LABORATORY PRACTICE FOR NONCLINICAL LABORATORY STUDIES

14. The authority citation for 21 CFR part 58 continues to read as follows:

Authority: 21 U.S.C. 342, 346, 346a, 348, 351, 352, 353, 355, 360, 360b–360f, 360h–360j, 371, 379e, 381; 42 U.S.C. 216, 262, 263b–263n.

15. Section 58.3 is amended by revising paragraph (e)(13) to read as follows:

* * * * *

(e) * * *

(13) An application for a biologics license, described in part 601 of this chapter.

* * * * *

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

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

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

17. 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, or a biologics license application.

* * * * *

18. 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, or a biologics license application. * * *

* * * * *

PART 310—NEW DRUGS

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

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

20. Section 310.4 is revised to read as follows:

§ 310.4 Biologics; products subject to license control.

(a) If a drug has an approved license 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.*), it is not required to have an approved application under section 505 of the act.

(b) To obtain marketing approval for radioactive biological products for human use, as defined in § 600.3(ee) of this chapter, manufacturers must comply with the provisions of 601.2(b) of this chapter.

21. 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

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

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

23. 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 or a biologics license application for a biological product submitted under the Public Health Service Act.

* * * * *

PART 316—ORPHAN DRUGS

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

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

25. 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 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

26. 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.

27. Section 600.3 is amended by revising paragraphs (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.

* * * * *

28. 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.

29. 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. * * *

30. 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.

* * * * *

31. Section 600.81 is amended by revising the first sentence to read as follows:

§ 600.81 Distribution reports.

The licensed manufacturer shall submit information about the quantity of the product distributed under the biologics license, including the quantity distributed to distributors. * * *

PART 601—LICENSING

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

Authority: 15 U.S.C. 1451–1561; 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; sec.122, Pub. L. 105–115, 111 Stat. 2322 (21 U.S.C. 355 note).

§ 601.1 [Removed]

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

34. 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 for introduction or delivery for introduction into interstate commerce; summaries of results of tests performed on the lot(s) represented by the submitted sample(s); specimens of the labels, enclosures, and containers, and if applicable, any Medication Guide required under part 208 of this chapter 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. The applicant shall also include a financial certification or disclosure statement(s) or both for clinical investigators as required by part 54 of this chapter. 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 (except for those products described in paragraph (b) of this section for which a new drug application is required), 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 December 20, 1999, 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]

35. Section 601.3 *License forms* is removed.

36. 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. * * *

37. 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 of this chapter,

(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 of this chapter, 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.

38. 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) of this chapter to revoke the license, or

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

39. 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]

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

41. 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 the 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.

42. 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 introduction or delivery for introduction into interstate commerce, except as provided in sections 505(i) and 520(g) of the Federal Food, Drug, and Cosmetic Act, as amended, and the regulations thereunder (21 CFR parts 312 and 812).

43. 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 it 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 ensure 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. * * *

44. Section 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. * * *

* * * * *

45. Section 601.26 is amended by revising the second sentence of the introductory text of paragraph (e), the first, fifth, and sixth 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. * * *

* * * * *

46. 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

47. 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.

48. 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.

* * * * *

49. 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) of this chapter) 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

50. 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.

51. 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. * * *

* * * * *

52. 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.

53. 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

54. 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.

55. 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:

* * * * *

56. 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.

57. 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.

* * * * *

58. 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.

* * * * *

59. 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.

* * * * *

60. 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) of this chapter and by an authorized representative of the Food and Drug Administration.

* * * * *

61. 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

62. 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.

63. 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.

* * * * *

64. 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 of this chapter, or from umbilical cord cells which shall be collected and prepared according to the manufacturer's biologics license application.

65. 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: August 30, 1999.

Jane E. Henney,

Commissioner of Food and Drugs.

Donna E. Shalala,

Secretary of Health and Human Services.

[FR Doc. 99–27159 Filed 10–19–99; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 25

Environmental Impact Considerations

CFR Correction

In Title 21 of the Code of Federal Regulations, parts 1 to 99, revised as of Apr. 1, 1999, page 240, § 25.32 is corrected by reinstating text missing from the end of paragraph (i) and the beginning of paragraph (j). In the eighth line of paragraph (i) ''percdditive'' is corrected to read ''percent additive'' and the following text is added between the words ''percent'' and ''additive'':

§ 25.32 Foods, food additives, and color additives.

* * * * *

(i) * * * –by–weight and is expected to remain with finished food–packaging material through use by consumers or when the substance is a component of a coating of a finished food–packaging material.

(j) Approval of a food * * *

* * * * *

[FR Doc. 99–55537 Filed 10–19–99; 8:45 am]

BILLING CODE 1505–01–D

DEPARTMENT OF THE INTERIOR

Minerals Management Service

30 CFR Parts 202 and 206

RIN 1010–AB57

Training Sessions on Gas Valuation for Indian Leases

AGENCY: Minerals Management Service, Interior.

ACTION: Notice of training sessions.

SUMMARY: The Minerals Management Service is offering six training sessions on our revised Indian gas valuation regulations that are effective January 1, 2000.

DATES: See **SUPPLEMENTARY INFORMATION** section for meeting dates.

ADDRESSES: See **SUPPLEMENTARY INFORMATION** section for meeting addresses.

FOR FURTHER INFORMATION CONTACT: Ms. Vicki Skinner, Royalty Valuation Division, Royalty Management Program, Minerals Management Service, P.O. Box 25165, MS 3152, Denver, CO 80225–0165; telephone number (303) 275–7241, fax number (303) 275–7227.

SUPPLEMENTARY INFORMATION: The dates and locations of the training sessions are as follows:

1. *Oklahoma City, OK:* November 1, 1999, 9 a.m. to 4 p.m., Central time. Clarion Airport West Hotel, 737 S. Meridian, Oklahoma City, OK 73108; telephone number (405) 942–8511.

2. *Tulsa, OK:* November 3, 1999, 9 a.m. to 4 p.m., Central time. Radisson Inn, 2201 N. 77th East Ave., Tulsa, OK 74115; telephone number (918) 835–9911.

3. *Farmington, NM:* November 16, 1999, 9 a.m. to 4 p.m., Mountain time. Holiday Inn, 600 E. Broadway, Farmington, NM 87401; telephone number (505) 327–9811.

4. *Houston, TX:* November 30, 1999, 9 a.m. to 4 p.m., Central time. Embassy Suites Hotel, 9090 Southwest Freeway, Houston, TX 77074; telephone number (713) 995–0123.

5. *Dallas, TX:* December 6, 1999, 9 a.m. to 4 p.m., Central time. Embassy Suites Market, 2727 Stemmons Freeway, Dallas, TX 75207; telephone number (214) 630–5332.

6. *Denver, CO:* December 15, 1999, 9 a.m. to 4 p.m., Mountain time. Holiday Inn, 14707 W. Colfax Ave., Golden, CO 80401; telephone number (303) 279–7611.

MMS published revised Indian gas valuation regulations in the **Federal Register** on August 10, 1999 (64 FR 43506). The revised regulations add alternative valuation methods to existing regulations to ensure that Indian lessors receive maximum revenues from their mineral resources as required by the unique terms of Indian leases and MMS's trust responsibility to Indian lessors. The revised regulations will also improve the accuracy of royalty payments at the time royalties are due.

If you produce gas from Indian lands, the new regulations affect you, and we strongly encourage you to attend one of these training sessions. Some of the topics that will be covered include: