Guidance for Industry

Cooperative Manufacturing Arrangements for Licensed Biologics

Additional copies of this guidance are available from the Office of Communication, Training and Manufacturers Assistance (OCTMA) (HFM-40), 1401 Rockville Pike, Rockville, MD 20852-1448 or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/cber/guidelines.htm.

For questions on the content of this guidance, contact OCTMA (Center for Biologics Evaluation and Research) at the phone numbers listed above and the Office of Pharmaceutical Science (Center for Drug Evaluation and Research) at 301-796-2400.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Center for Drug Evaluation and Research
November 2008

OMB Control No. 0910-0629
Expiration Date: 03/30/2011
See additional PRA statement in Section VII of this guidance

Contains Nonbinding Recommendations

Guidance for Industry

Cooperative Manufacturing Arrangements for Licensed Biologics

Additional copies of this guidance are available from:

Office of Communication, Training and Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448
Phone: 800-835-4709 or 301-827-1800
Internet: http://www.fda.gov/cber/guidelines.htm
or
Office of Training and Communication
Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, rm. 2201
Silver Spring, MD 20993-0002
Phone: 301-796-3400
Internet: http://www.fda.gov/cder/guidance/index.htm

Table of Contents

Guidance for Industry

Cooperative Manufacturing Arrangements for Licensed Biologics

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. SCOPE

The development of complex and highly specialized technology and equipment for the manufacture of biological products has fostered the emergence of many companies that perform only limited aspects of manufacturing processes. Consequently, many manufacturers are interested in sharing or contracting parts of manufacturing in order to facilitate product development and manufacturing flexibility. Cooperative manufacturing arrangements enhance the development of new products.

Therefore, we, the Food and Drug Administration (FDA), are issuing this guidance on cooperative manufacturing arrangements applicable to biological products subject to licensure under section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262). This document is issued jointly between the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER). This guidance describes our current thinking on licensing strategies for meeting the increased need for flexible manufacturing arrangements. Since cooperative manufacturing arrangements can take a considerable amount of time to develop, this guidance may also be useful for planning purposes in the early phases of product development.

FDA registered manufacturers of biological products and transfusion services may also choose to follow this guidance.

This guidance supersedes "FDA's Policy Statement Concerning Cooperative Manufacturing Arrangements for Licensed Biologics" published in the *Federal Register* of November 25, 1992 (57 FR 55544) (Ref. 1), and finalizes the draft guidance of the same title dated July 2007, which revised the draft guidance of the same title dated August 1999.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited.

The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. INTRODUCTION

Under section 351(a)(2)(C) of the PHS Act, FDA will approve a biologics license application (BLA) on the basis of a demonstration that the biological product is safe, pure, and potent, and that the facility in which the biological product is manufactured meets standards designed to assure that the biological product continues to be safe, pure, and potent.[1] Section 351(c) of the PHS Act authorizes FDA to conduct a pre-approval inspection of the facility in which the product is manufactured.

FDA's biologics regulations define "manufacturer" as "any legal person or entity engaged in the manufacture of a product subject to license under the PHS Act," including "any legal person or entity who is an applicant for a license where the applicant assumes responsibility for compliance with the applicable product and establishment standards" (21 Code of Federal Regulations (CFR) 600.3(t)). A manufacturer thus includes a license applicant, who may or may not own the facilities engaged in significant manufacturing steps, when such an applicant assumes responsibility for compliance with the applicable product and establishment standards, including, but not limited to, 21 CFR Parts 210, 211, 600 through 680, and 820.

"Manufacture" is defined as "all steps in propagation or manufacture and preparation of products and includes but is not limited to filling, testing, labeling, packaging, and storage by the manufacturer" (21 CFR 600.3(u)).

A manufacturer of a biological product must demonstrate responsibility for the manufacturing process as described in its BLA (21 CFR 600.3(t)). For example, a manufacturer must avoid introduction of contaminants during production (21 CFR 610.13).

Adequate supervision and control over the manufacture of a biological product has often been achieved by a single manufacturer performing all steps in the production of a product within facilities owned and operated by that manufacturer. However, as described in our 1992 policy statement on cooperative manufacturing arrangements, we have accepted various alternative arrangements involving more than one manufacturer. These alternative manufacturing arrangements include short supply and divided manufacturing, as well as shared and contract manufacturing arrangements. Certain regulatory requirements are partially described for short supply in 21 CFR 601.22 and for divided manufacturing in 21 CFR 600.12(e) and 610.63.

We previously published guidance that clarified that small scale or pilot facilities are eligible for licensure provided they are fully qualified and validated, operate in accordance with CGMP

[1] FDA has interpreted the definition of the term "potency" in 21 CFR 600.3(s) to include effectiveness. Furthermore, biological products also meet the definition of "drug" or "device" under the Federal Food, Drug, and Cosmetic Act (FDC Act), and therefore are also subject to certain requirements in the FDC Act and its implementing regulations such as current good manufacturing practice (CGMP) provisions.

requirements, and otherwise comply with applicable laws and regulations (Ref. 2). The principles described in this guidance are designed to assure that the safety, purity, and potency of biological products will not be compromised as a result of innovative, flexible manufacturing arrangements.

III. SHORT SUPPLY ARRANGEMENTS

Under 21 CFR 601.22 if a product is in short supply, a licensed biologic manufacturer may obtain the initial and partially-manufactured version of the product from unlicensed facilities when the following conditions are met:

- manufacturing at the unlicensed location is limited to the initial and partial manufacturing of a product for shipment solely to the licensee;
- the name and place of the unlicensed location are registered with FDA (see e.g., registration and listing provisions in 21 CFR Parts 207 and 607);
- the licensed manufacturer files an application explaining that the product is in short supply due either to peculiar growth requirements of the organism involved or to the scarcity of the source required for manufacturing purposes;
- FDA makes a finding agreeing with the licensed manufacturer's explanation; and
- the licensed manufacturer can ensure that, through inspections, testing, or other procedures, the product made at the unlicensed facility will be made in full compliance with applicable regulations.

The short supply provisions have limited applicability. Although some industries, such as those involving recovered plasma, deal with these provisions more often, they are generally used in unusual circumstances where the licensed product is scarce or growth requirements are so peculiar that production is infrequent.

Licensed manufacturers may use these provisions to obtain source materials only. Such source materials undergo specified limited processing only. Examples of materials that might be obtained under short supply include:

- certain source materials used in producing allergenic extracts;
- specific types of human plasma containing rare antibodies;
- venoms used in producing antitoxins and antivenins;
- recovered plasma;
- unlicensed Red Blood Cells used to manufacture blood bank reagents; and
- materials made in non-human animals.

Suppliers of source materials are subject to FDA inspection under section 704(a) of the FDC Act.

A licensed manufacturer desiring to enter into a short supply arrangement should either file the required manufacturing process information and assurances with its original BLA under

21 CFR 601.2 or submit it to either CBER or CDER, as appropriate, as a change to an approved application as described in 21 CFR 601.12.

IV. DIVIDED MANUFACTURING ARRANGEMENTS

Divided manufacturing is an arrangement in which two or more manufacturers, each registered with FDA in accordance with 21 CFR Parts 207, 607, or 807 as applicable, and licensed to manufacture a specific biological product in its entirety, participate jointly in the manufacture of that product.

A. General

We recommend that manufacturers desiring to enter into a divided manufacturing arrangement describe the role of each manufacturer in an original application or supplement(s) to the manufacturers' BLAs, as appropriate. We recommend that the application(s) or supplement(s) describe the steps to be performed at each facility and include the labeling that will be used on any intermediate and final products.

Factors we consider in determining whether to approve these submissions include, but are not limited to:

- conformance to licensed manufacturing procedures and specifications;
- equivalence of the intermediate products;
- ability of the manufacturers to demonstrate the stability of the intermediate product during shipment; and
- adequacy of intermediate and finished product labels and labeling.

Each licensed manufacturer in a divided manufacturing arrangement must notify the appropriate FDA Center regarding proposed changes in the manufacture, testing, or specifications of its product, in accordance with 21 CFR 601.12 (see Refs. 3, 4, and 5). Each licensed manufacturer that proposes such a change should inform other participating licensed manufacturer(s) of the proposed change.

B. Recordkeeping Requirements

All manufacturers participating in a divided manufacturing arrangement must comply with the recordkeeping requirements of 21 CFR Parts 210 and 211, and 21 CFR 600.12(e) as applicable, and the other applicable CGMP regulations.

C. Labeling

The name, address, and license number of each participating licensed manufacturer must appear on the package label, and on the label of the container if capable of bearing a full label (21 CFR 610.63). FDA's experience has shown that the display of names,

addresses, and license numbers of all participating manufacturers on container labels has not always been feasible, particularly in the case of multiple party manufacturing arrangements.

FDA is concerned that the appearance of multiple names and addresses on the outer label affixed to a package may cause confusion and limit the prominence of more important labeling statements. Under 21 CFR 600.3(cc), the term "package" is defined to include the package insert. To comply with 21 CFR 610.63, we recommend that you do the following:

- place the name, address, and license number of the manufacturer of the finished dosage form and the manufacturer responsible for reporting adverse events of the biological product on the outer label affixed to the package; and
- place the names, addresses, and license number(s) of **all** manufacturer(s) participating in the divided manufacturing arrangement in the product package insert.

A licensed intermediate product will be approved for further manufacturing use, and accordingly, we recommend that the phrase, "for further manufacturing use" be included as part of the proper name. If included as part of the proper name, the phrase must appear on the label affixed to each package containing the product (21 CFR 610.61), as well as the container label if capable of bearing a full label (21 CFR 610.60).

Blood products are often the subject of divided manufacturing arrangements. Under 21 CFR 606.121(c)(2), a registration number must also be on the container label for blood and blood components for transfusion, and if a licensed product, the license number of each manufacturer.

V. SHARED AND CONTRACT MANUFACTURING ARRANGEMENTS

We recognize that a biologic manufacturer seeking licensure may not have the capability or may choose not to perform all operations at an establishment under its legal ownership. Where a license applicant decides not to manufacture the biological product in its entirety (beginning with raw materials through final formulation, filling, packaging, and labeling), the license applicant may seek to enter into either a shared or contract manufacturing arrangement with one or more manufacturers, as described below.

A. Shared Manufacturing Arrangements

Shared manufacturing is an arrangement in which two or more manufacturers are licensed and responsible for specific aspects of the manufacture of a product but none is licensed for all aspects of the manufacture of the product.

A common shared manufacturing arrangement is one in which one manufacturer is responsible for an intermediate product and another for the final product.

1. General

A participating manufacturer may perform the specified manufacturing steps and/or contract with another entity(ies) and assume responsibility for compliance with the applicable product and establishment standards as described for an applicant in 21 CFR 600.3(t). A participating manufacturer that performs (or is responsible for the performance of) significant product manufacturing is considered eligible for separate licensure under this arrangement.

Significant manufacturing steps that may affect a product's safety, purity, or potency and, which we have considered adequate for separate licensure include, but are not limited to, the following:

- inoculation of vessels or animals for production;
- cell culture production and characterization;
- fermentation and harvesting;
- isolation;
- purification;
- physical and chemical modifications;
- required infectious disease testing of blood and blood components; and
- blood donor recruitment and maintenance of donor deferral registries.

Manufacturing steps that would not by themselves ordinarily warrant separate licensing, even though important to the purity and integrity of the final product, include:

- chemical and biological testing other than blood infectious disease testing;
- formulation;
- sterile filling;
- lyophilization; and
- labeling.

When any of these steps are proposed to be performed by another manufacturer, we will generally view it as a procedure that may be performed under a contractual arrangement (see section V.B below). However, we also recognize that companies may conceive and develop innovative products through extensive preclinical and clinical testing, but choose to limit their participation in product manufacturing. Therefore, we will consider a manufacturer eligible for separate licensure if that manufacturer is both instrumental in product development and performs (or is responsible for the performance of) several final manufacturing

steps, such as formulation, sterile filling, lyophilization, labeling, packaging, and final release testing.

Manufacturers desiring to enter into a shared manufacturing arrangement must register with FDA in accordance with registration and listing provisions in 21 CFR Part 207, 607, or 807, as applicable.

2. BLAs

Each manufacturer must submit a separate BLA describing the manufacturing facilities and operations applicable to the preparation of that manufacturer's biological substance or product (21 CFR 601.2(a)). Each BLA must meet the requirements of 21 CFR 601.2 and fully describe:

- the extent of manufacturing and testing performed by that participating manufacturer;
- the specifications;
- the storage and shipping conditions;
- the manufacturing methods;
- stability data;
- product lots available for examination; and
- the labeling that will accompany that manufacturer's product.

We recommend that all license applications/supplements that pertain to a particular product to be manufactured under a shared manufacturing arrangement be submitted concurrently (i.e., on the same date) so that we can conduct a complete review of the product, since we will depend on information contained in all related applications when determining whether to issue the biologics license.

Lack of one or more related applications may be a basis for a refusal to file action (Ref. 6).

Please consult the appropriate guidance document regarding submission of chemistry, manufacturing, and controls information for technical guidance on the content and format of a license application (Refs. 7-13).

a. Intermediate products

A common shared manufacturing agreement is one in which one manufacturer is responsible for an intermediate product and another for the final product. An application/supplement for an intermediate product licensed "for further manufacturing use" must include, in addition to other information in a BLA, the criteria used to determine lot-by-lot acceptability of the product (21 CFR 601.2), including:

- sterility (or bioburden);
- stability;
- product characterization;
- potency; and
- purity specifications.

Manufacturers of all intermediate products must demonstrate that their products will consistently meet established specifications (21 CFR 601.2).

We intend to accept only those BLAs/supplements for biological products intended for further manufacture in a shared manufacturing arrangement that specify the licensed manufacturer or manufacturers to which the intermediate product will be shipped. These BLAs/supplements will be approved only after demonstration of safety and efficacy of the final product.

b. Final product

We will accept only those BLAs/supplements for final products in a shared manufacturing arrangement that specify the source(s) of the intermediate product(s) to be used. The approval of the final product will be dependent upon established criteria for receipt and acceptance of the intermediate(s).

We expect the manufacturer that prepares (or is responsible for the preparation of) the product in final form for commercial distribution to assume primary responsibility for providing data demonstrating the safety, purity, and potency of the final product. We also expect the licensed finished product manufacturer to be primarily responsible for any postapproval obligations, such as postmarketing clinical trials, additional product stability studies, complaint handling, recalls, postmarket reporting of the dissemination of advertising and promotional labeling materials as required under 21 CFR 601.12(f)(4) and adverse experience reporting. We recommend that the final product manufacturer establish a procedure with other participating manufacturer(s) to obtain information in these areas.

3. Responsibilities of Each Participating Manufacturer

Each licensed manufacturer in a shared manufacturing arrangement must notify the appropriate FDA center regarding proposed changes in the manufacture, testing, or specifications of its product (21 CFR 601.12; see Refs. 3, 4 and 5); and

should notify other participating licensed manufacturer(s) of such proposed change.

We expect license manufacturers to have the technical knowledge and expertise needed to identify manufacturing problems or deviations and take responsibility for conducting preventive and/or corrective action to ensure the safety and effectiveness of the product (21 CFR 211.25).

All manufacturers participating in a shared manufacturing arrangement must also comply with the recordkeeping requirements of 21 CFR Parts 210 and 211, and the other applicable CGMP regulations.

Each manufacturer in a shared manufacturing arrangement who holds a biological product license is responsible for reporting biological product deviations that occurred when the product was in its control (21 CFR 600.14).

4. Labeling

The labeling for products prepared in a shared manufacturing arrangement must comply with applicable provisions of 21 CFR 610.60 through 610.67, including identification of all participating licensed manufacturers.

FDA interprets 21 CFR 610.63 for divided manufacturing arrangements to apply to products manufactured by more than one licensed manufacturer, including shared manufacturing arrangements. In such cases, the package label provisions of that section may be met by placing the name, address, and license number of the final product manufacturer and the manufacturer responsible for reporting adverse events on the outer label affixed to the package, and by placing the names, addresses, and license numbers of manufacturers participating in the shared manufacturing arrangement in the product package insert. The end user may then identify contributing manufacturing firms more efficiently.

Since a licensed intermediate product will be approved for further manufacturing use, we recommend that the phrase, “for further manufacturing use” be included as part of the proper name. If included as part of the proper name, the phrase must appear on the label affixed to each package containing the product (21 CFR 610.61), as well as the container label, if capable of bearing a full label (21 CFR 610.60).

B. Contract Manufacturing Arrangements

For the purposes of this document, contract manufacturing refers to a situation in which a license manufacturer establishes a contract with another entity(ies) to perform some or all of the manufacture of a product as a service to the license manufacturer. This includes,

for example, required infectious disease testing of blood and blood components conducted by licensed blood establishments for another manufacturer.

A contract facility that is engaged in significant manufacturing is not required to be separately licensed, as is the case in a Shared Manufacturing Arrangement.

1. Responsibilities of License Manufacturer

A license manufacturer that establishes a contract with another entity to perform some or all of the manufacture of a product is responsible for:

- the safety, purity, and potency of the product (PHS Act; 21 CFR Parts 600 through 680);
- ensuring that manufacture of the product complies with the provisions of the BLA and the applicable regulations, including, but not limited to, 21 CFR Parts 210, 211, 600 through 680, and 820; and
- compliance with both product and establishment standards.

Product and establishment standards, and applicable regulations may include, but are not limited to, the following:

- product release and in-process specifications (21 CFR 211.110 and 610.1);
- adverse experience reports, biological product deviation reports, medical device reporting systems (21 CFR 600.14, 600.80, 606.171, 803.20, 803.50, and 803.53);
- production and process controls (21 CFR Part 211.100 through 211.115);
- reporting changes to the production process and all facilities as required by 21 CFR 601.12;
- maintenance of master production records and control records for drug products and device master records and device history records for devices (21 CFR 211.186, 820 181, 820.184);
- laboratory controls, including testing and release for distribution (21 CFR 211.160 through 176);
- submission of protocols and samples for lot release, where applicable (21 CFR 610.2);
- labeling (21 CFR Part 201, 610.60 through 610.62, 606.120 through 122, 660.2(c), 660.28, 660.35, 660.45, 660.55, and Parts 801 and 809);
- systems to ensure continued CGMP functioning of equipment and facilities (21 CFR Part 211, Subpart D);
- environmental monitoring (21 CFR 211.42(c)(10)(iv));
- infectious disease testing of blood and blood components (21 CFR 610.40); and
- training of personnel (21 CFR 211.25 and 600.10).

The contract manufacturer should share with the license manufacturer all important proposed changes to production and facilities (including introduction of new products or at inspection). The license holder is responsible for reporting these changes to FDA (21 CFR 601.12; see Refs. 3, 4, and 5).

2. Responsibilities of the Contract Manufacturer

Because the contract manufacturer is engaged in the manufacture of a drug or device, it must comply with applicable provisions of the FDC Act (21 U.S.C. 301 et. seq.) and applicable regulations.

Contract facilities are subject to FDA inspection under section 351(c) of the PHS Act and section 704(a) of the FDC Act. Facilities performing contract operations for biological products must register with FDA in accordance with registration and listing provisions in 21 CFR Parts 207, 607, or 807.

Because the license manufacturer must ensure that the contract site complies with applicable product and establishment standards, the license manufacturer should have access to floor plans, equipment validation, and other production information. The license manufacturer must have a procedure in place for receiving information from the contract facility on all deviations, complaints, and adverse events (21 CFR 600.14(a); 606.171(a); 803.10).

We reiterate that the contract manufacturer should fully inform the license manufacturer of the results of all tests and investigations regarding or possibly having an impact on the product.

We remind the license manufacturer that the license manufacturer assumes responsibility for compliance with the applicable product and establishment standards (21 CFR 600.3(t)). Therefore, if the license manufacturer enters into an agreement with a contract manufacturing facility, the license manufacturer must ensure that the facility complies with the applicable standards. An agreement between a license manufacturer and a contract manufacturing facility normally includes procedures to regularly assess the contract manufacturing facility's compliance. These procedures may include, but are not limited to, review of records and manufacturing deviations and defects, and periodic audits.

The license manufacturer should be aware that all contract manufacturing locations must be in compliance with CGMP regulations and are subject to inspection from the time of the submission. We also recommend that the license manufacturer obtain assurance from the contractor that any FDA list of inspectional observations will be shared with the license manufacturer to allow evaluation of its impact on the purity, potency, and safety of the license manufacturer's product.

In accordance with 21 CFR 200.10, FDA may disclose any information obtained during the inspection of a contract facility having a specific bearing on compliance with the FDC Act to the license manufacturer.

Compliance actions, such as license revocation, may be considered against the license manufacturer for failure of the contract manufacturer to comply with CGMP regulations or otherwise fail to fulfill requirements of the license for which the contract manufacturer is contractually responsible.

Please consult the appropriate guidance document regarding submission of chemistry, manufacturing, and controls information for technical guidance on the suggested content and format of a license application, including a complete description of all contract manufacturing operations (Refs. 7-13).

For each contract arrangement, the license manufacturer's BLA/supplement should describe the product subject to contract manufacturing, including:

- the product stability and the manner of shipment to and from the contract facility;
- the responsibilities of each participating entity;
- contract manufacturers' names, address, license number, if applicable, and registration number; and
- a list of all standard operating procedures applicable to the contract arrangement.

Contract firms that do not wish to provide all necessary information to the license manufacturer should consider a shared manufacturing arrangement.

3. Master Files

We recommend that a license manufacturer cross reference a contract manufacturing facility's Master Files only in circumstances involving certain proprietary information of the contract manufacturer, such as:

- a list of all products manufactured in a contract facility (in this situation the license manufacturer should be kept informed of the types or categories of all products manufactured in the contract facility).
- noncompendial test procedures (standard operating procedures) (provided there is assurance that both the license manufacturer and FDA will be informed of all changes in these procedures).

The BLA/supplement(s) may also refer to Master Files for information regarding containers and closures.

4. Labeling

The labeling for final products prepared under a contractual agreement must comply with the applicable provisions of 21 CFR 610.60 through 610.65, and 21 CFR Parts 201 and 809, where applicable. Because the contract facilities are considered to be under the control of the license holder, specific identification of the contractor in the product labeling is not required.

We recommend that the labeling for an intermediate product intended for shipment to or from a contract facility include a statement that it is intended for further manufacture. We recommend that licensed intermediate products include "for further manufacture" as part of the proper name. If included as part of the proper name, the phrase must appear on the label affixed to each package containing the product (21 CFR 610.61), as well as the container label, if capable of bearing a full label (21 CFR 610.60). Licensed intermediates must also bear a U.S. license number (21 CFR 610.61).

VI. REFERENCES

1. FDA's Policy Statement Concerning Cooperative Manufacturing Arrangements for Licensed Biologics, November 25, 1992, 57 FR 55544.

2. FDA Guidance Document Concerning Use of Pilot Manufacturing Facilities for the Development and Manufacture of Biological Products, July 11, 1995, 60 FR 35750.

3. Guidance for Industry: Changes to an Approved Application: Biological Products, July 1997.

4. Guidance for Industry: Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products, July 1997.

5. Guidance for Industry: Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture, July 2001.

6. Center for Biologics Evaluation and Research Refusal to File (RTF) Guidance for Product License Applications (PLAs) and Establishment License Applications (ELAs), July 12, 1993.

7. 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," May 1999.

8. Guidance for Industry: On the Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for an Allergenic Extract or Allergen Patch Test, April 1999.

9. Guidance for Industry: Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Biological *In Vitro* Diagnostic Product, March 1999.

10. 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, February 1999.

11. Guidance for Industry: Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Vaccine or Related Product, January 1999.

12. Guidance for the Submission of Chemistry, Manufacturing, and Controls Information and Establishment Description for Autologous Somatic Cell Therapy Products, January 1997.

13. 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, August 1996.

VII. PAPERWORK REDUCTION ACT OF 1995

This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520).

We believe that the information collection provisions in the guidance do not create a new burden for respondents. We believe the reporting and recordkeeping provisions are part of usual and customary business practices. Licensed manufacturers would have contractual agreements with participating licensed manufacturers, final product manufacturers, and contract manufacturers, as applicable for the type of cooperative manufacturing arrangement, to address all these information collection provisions. Send comments regarding this burden estimate or suggestions for reducing this burden to:

Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike, Suite 200N
Rockville, MD 20852-1448

This guidance also refers to previously approved collections of information found in FDA regulations at parts 201, 207, 211, 600, 601, 606, 607, 610, 660, 803, and 807 (21 CFR parts 201, 207, 211, 600, 601, 606, 607, 610, 660, 803, and 807). The collections of information in §§ 606.121, 606.122, and 610.40 have been approved under OMB Control No. 0910-0116; § 610.2 has been approved under OMB Control No. 0910-0206; §§ 600.12(e) and 600.80 have been approved under OMB Control No. 0910-0308; §§ 601.2(a), 601.12, 610.60, 610.61, 610.62, 610.67, 660.2(c), 660.28(a) and (b), 660.35(a), 660.35(c) through (g), 660.35(i) through (m), 660.45, and 660.55(a) and (b) have been approved under OMB Control No. 0910-0338; §§ 803.20, 803.50, and 803.53 have been approved under OMB Control No. 0910-0437; and §§ 600.14 and 606.171 have been approved under OMB Control No. 0910-0458. The current good manufacturing practice regulations for finished pharmaceuticals (part 211) have been approved under OMB Control No. 0910-0139; the establishment registration regulations (parts 207, 607, and 807) have been approved under OMB Control Nos. 0910-0045, 0910-0052, and 0910-0387; and the labeling regulations (part 201) have been approved under OMB Control Nos. 0910-0340 and 0910-0370.

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 No. The OMB Control No. for this information collection is 0910-0629 (Expires 09/30/2011).