DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 92N–0374]

FDA's Policy Statement Concerning Cooperative Manufacturing Arrangements for Licensed Biologics

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that it is setting forth a policy statement entitled, "Manufacturing Arrangements for Licensed Biologics." This FDA policy describes innovative arrangements among establishments who wish to cooperate in the manufacture of a licensed biological product. The intent of this policy is to assist manufacturers in the production of both conventional and biotechnology-derived products.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: For information on this notice: Daniel Kearns, Center for Biologics Evaluation and Research (HFB–130), Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892, 301–295–8188.

For substantive questions on the policy statement: Sharon Risso, Center for Biologics Evaluation and Research (HFB–240), Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892, 301–295–8431.

SUPPLEMENTARY INFORMATION: FDA is setting forth a policy statement entitled "Manufacturing Arrangements for Licensed Biologics." This policy statement is intended to advise current and potential manufacturers of biological and biotechnology products subject to licensure under section 351 of the U.S. Public Health Service Act of available cooperative manufacturing arrangements.

Cooperative manufacturing arrangements include short supply, divided manufacturing, shared manufacturing, and contract manufacturing arrangements. FDA has approved a variety of cooperative manufacturing arrangements for biological products in the past (see the **Federal Register** of November 3, 1983, 48 FR 50795). This statement describes the current licensing policy of the Center for Biologics Evaluation and Research (CBER) for meeting the increased demand for flexible manufacturing arrangements. This policy statement provides information about, but does not set forth requirements for, cooperative manufacturing arrangements. FDA does not intend that this policy statement be comprehensive and further cautions that not all information is applicable to all situations.

This policy statement is intended as guidance to manufacturers of new biological products, to those already engaged in cooperative manufacturing arrangements, and to those considering changing their present manufacturing arrangements.

This policy statement may be useful to applicants in submitting product license applications (PLA's), establishment license applications (ELA's), and applications for license amendments. Applicants may follow the guidance or may choose to use alternate procedures even though they are not provided for in the policy statement. If an applicant chooses to use alternate procedures, the applicant may wish to discuss the matter further with the agency to prevent expenditure of money and effort on activities that may later be determined to be unacceptable by FDA.

This guidance does not bind the agency and does not create or confer any rights, privileges, or benefits for or on any person.

Interested persons are encouraged to use this opportunity to submit comments on the policy statement. These comments will be considered in determining whether amendments to, or revisions of, the policy statement are warranted. Two copies of any comments are to be submitted, except that individuals may submit one copy. Requests and comments should be identified with the docket number found in brackets in the heading of this document. Comments received are available for

public examination in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday.

Policy Statement on "Manufacturing Arrangements For Licensed Biologics"

Scope

The development of complex and highly specialized technology and equipment for products of biotechnology has fostered the emergence of many establishments that are capable of performing only limited aspects of manufacturing processes. Restricting issuance of biologic licenses solely to legal entities capable of performing all steps in manufacturing could impede the development of new technology products which involve multiple manufacturers. Therefore, FDA is issuing this notice to provide guidance to interested persons on cooperative manufacturing arrangements applicable to biological products.

Discussion

Section 351(d) of the U. S. Public Health Service Act (42 U.S.C. 262 (d)) and the regulations promulgated thereunder in part 601 (21 CFR part 601), provide that an establishment may obtain a license to manufacture a biological product only upon a showing that it has the capability to manufacture a safe, pure, and potent biological product within the facility under consideration. No establishment license may be issued unless a product license is issued simultaneously with the establishment license and such product is available for examination at the facility intended for licensure (§ 601.10(b)). Such examination is normally conducted during the prelicensing inspection.

In order to establish adequate control over the manufacturing process for a biological product, including avoidance of introduction of contaminants during production and assurance of lot-to-lot consistency, an applicant for a biological product license must demonstrate supervision and control over the entire manufacturing process. "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)).

Demonstration of adequate supervision and control over the manufacturing of a biological product has generally been documented by a single manufacturer performing all steps in the production of a product

within facilities owned and operated by that manufacturer. However, FDA has permitted certain alternate arrangements involving more than one manufacturer. These alternate manufacturing arrangements include short supply and divided manufacturing, as partially described in the current biological regulations, § 600.12(e) (21 CFR 600.12(e)), § 601.22 (21 CFR 601.22), and § 610.63 (21 CFR 610.63). In addition, FDA has approved several licenses that include shared and contract manufacturing arrangements. FDA initially introduced the concept of shared manufacturing for biological products in the **Federal Register** of November 3, 1983 (48 FR 50795), when FDA announced its policy on "Licensing of a Biological Monoclonal Antibody Product Prepared by Hybridoma Technology." This notice will provide guidance on obtaining FDA approval for short supply, contract, divided, and shared manufacturing arrangements for biological products.

The principles described in this document are designed to assure that biological product safety, purity, and potency will not be compromised as a result of innovative manufacturing arrangements.

Short Supply Arrangements

Under § 601.22, a licensed biologic manufacturer may obtain certain materials which are manufactured at unlicensed facilities when the following conditions are met: (1) Manufacturing at the unlicensed facility will be limited to the initial and partial manufacturing of a product for shipment solely to the licensee; (2) the unlicensed manufacturer is registered with FDA in accordance with registration and listing provisions in part 207 (21 CFR part 207); (3) the product made at the unlicensed facility is in short supply due either to peculiar growth requirements or scarcity of the source organism required for manufacturing; and (4) the licensed manufacturer can assure that, through inspections, testing, or other arrangements, the product made at the unlicensed facility will be made in full compliance with applicable regulations.

The short supply provisions have limited applicability. Licensed manufacturers may use these provisions to obtain source materials only. Such source materials should have undergone only the limited processing necessary for shipment. These provisions have been and will be limited to use in unusual circumstances where the source material is scarce or growth requirements so peculiar that production is

uncommon. Examples of materials that might be obtained under short supply include certain pollens and insects used in producing allergenic extracts and human plasma containing rare antibodies.

The license applicant desiring to enter into a short supply agreement should either file the required information and assurances with its initial product application or submit a descriptive amendment to an approved application, whichever is applicable, for CBER review and approval.

Divided Manufacturing Arrangements

Divided manufacturing is an arrangement in which two manufacturers, each registered with FDA in accordance with part 207 and licensed to manufacture a specific biological product in its entirety, participate jointly in the manufacture of the product. Manufacturers desiring to enter into a divided manufacturing arrangement should describe the role of each manufacturer in procedures submitted as amendments to the two product license applications. The amendments should describe the steps to be performed at each facility and the labeling that will be used on any intermediate and end products. Among the factors that FDA intends to assess in determining whether to approve such amendments are conformance to licensed manufacturing procedures, the ability of the manufacturers to demonstrate the stability of the intermediate product during shipment, the adequacy of intermediate and finished product labels and labeling, and the ability to demonstrate acceptable methods of handling finished product adverse reaction and defect reports.

Current biologics regulations prescribe recordkeeping requirements for each party in a divided manufacturing arrangement (see § 600.12(e)). Other regulations require that the name, address, and license number of each participating licensed establishment appear on the package label, and on the label of the container if capable of bearing a full label (see § 610.63). With respect to § 610.63, FDA's experience has shown that the display of the 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. In addition, 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. Accordingly, FDA will consider the package label provisions of § 610.63 to be met by placing the name,

address, and license number of the finished dosage form manufacturer on the outer label affixed to the package and by placing the names, addresses, and license numbers of preceding intermediate product manufacturers participating in the divided manufacturing arrangement in the description section of the product package insert. The labeling for an intermediate product should include a statement that it is intended for further manufacture.

Shared and Contract Manufacturing Arrangements

The FDA recognizes that a biologic manufacturer seeking licensure may not always have the capability to perform all operations at a manufacturing establishment under its legal ownership. Where a license applicant does not have the capability to manufacture the biological product in its entirety (beginning with raw materials through final formulation, filling, packaging, and labeling), it may be possible to enter into a shared or contractual arrangement with one or more manufacturers, as described below.

Shared Manufacturing Arrangements

Shared manufacturing is an arrangement in which two or more manufacturers perform different aspects of the manufacture of a product, neither performs nor is licensed to perform all aspects of the manufacture, and each manufacturer holds product and establishment license applications. Each participant in a shared manufacturing arrangement should perform significant product manufacturing which results in the preparation of an identifiable and stabilized intermediate or end product and/or have been instrumental in product development. FDA intends to consider manufacturers eligible for separate establishment and product licenses when they perform critical manufacturing steps on the product which may alter structure and specificity and that may affect its safety, purity, or potency. These steps may include, but are not limited to, the following: (1) Inoculation of vessels or animals for production, (2) cell culture production and characterization, (3) fermentation and harvesting, (4) isolation, (5) purification, and (6) physical and chemical modifications. Manufacturing steps such as chemical and biological testing, formulation, sterile filling, lyophilization, and labeling, while important to the purity and integrity of the end product, are not manufacturing processes which by themselves would ordinarily warrant separate establishment and product licenses. Rather, when these steps are proposed to be performed by another manufacturer, they

will generally be viewed as procedures that may be performed under a contractual arrangement. See section entitled "Contract Manufacturing Arrangements," below.

However, FDA recognizes, especially in the area of biotechnology, that companies may conceive and develop innovative products through extensive preclinical and clinical testing, but have physical production capabilities that severely limit their participation in product manufacturing. Such companies generally have the capability to perform end stage processing and possess extensive technical knowledge and expertise to identify manufacturing problems at any stage in the manufacture of the product. Therefore, FDA intends to consider eligible for separate establishment and product licensure a company that is both instrumental in product development and that conducts several final manufacturing steps; e.g., a firm that conducts clinical trials to establish safety, effectiveness, and product stability, and that conducts 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 part 207 and should submit product and establishment license applications to CBER for concurrent review. Each manufacturer should submit separate establishment and product license applications describing the manufacturing facilities and operations applicable to the preparation of that manufacturer's biological product. Each application should conform to the provisions contained § 601.2(a) and should describe fully the extent of manufacturing and testing performed by that participating manufacturer, the storage and shipping conditions, and the labeling that will accompany that manufacturer's product.

A manufacturer engaged in the manufacture of an intermediate product should include in its license application the criteria used to determine lot-by-lot acceptability of its product, including sterility (or bioburden), stability, product characterization, potency, and purity specifications, and any other pertinent information applicable to the manufactured product. Manufacturers of all intermediate products should demonstrate that their component biological products will consistently meet established specifications. Each licensed manufacturer in a shared manufacturing arrangement must notify CBER regarding proposed changes in the manufacture or testing of its component biological product, in accordance with § 601.12,

and should also notify the other participating manufacturers. Manufacturers participating in a shared manufacturing arrangement must comply with recordkeeping requirements of § 600.12(e).

FDA intends to accept only those license applications 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, and approve such applications only after demonstration of safety and efficacy of the end product. Similarly, FDA intends to accept only those license applications for end products in a shared manufacturing arrangement that specify the source(s) of the licensed product(s) to be used. The approval of the end product will be dependent upon a demonstration of established specifications for receipt and acceptance of the intermediate(s). Any proposed changes in the source of the intermediate or its specifications or the manufacturer of the end product or its specifications, will require an amendment to the product license application(s) in accordance with § 601.12.

FDA expects the manufacturer that prepares the product in final form for commercial distribution to undertake primary responsibility for providing data demonstrating the purity, potency, safety, and effectiveness of the end product. The manufacturer of the end product should demonstrate the technical knowledge and expertise to identify any manufacturing problems or errors occurring at any stage in the manufacture of the product.

FDA expects the licensed end product manufacturer to be primarily responsible for any post-approval obligations, such as additional clinical trials, product stability studies, recall, and adverse product experience reporting.

The labeling for products prepared in a shared manufacturing arrangement must conform to applicable portions of §§ 610.60 through 610.65 (21 CFR 610.60 through 610.65), including identification of all participating licensed manufacturers. Consistent with FDA's interpretation of § 610.63 for divided manufacturing discussed under the section on "Divided Manufacturing Arrangements" above, with respect to products manufactured by more than one licensed establishment, the package label provisions of that section may be met by placing the name, address, and license number of the end product manufacturer on the outer label affixed to the package and by placing the names, addresses, and license numbers of

preceding intermediate product manufacturers participating in the shared manufacturing arrangement in the description section of the product package insert. The labeling for an intermediate product should include a statement that it is intended for further manufacture.

Contract Manufacturing Arrangements

Where a licensed manufacturer lacks the capability to perform all operations at an establishment it owns, but the manufacturing steps proposed to be performed by another manufacturer are not those that would ordinarily warrant separate licensure, nor has the other manufacturer been instrumental in product development, a contract manufacturing arrangement may be available. A licensed manufacturer may contract for the performance of certain manufacturing operations at facilities belonging to a separate legal entity upon receiving approval of a written amendment request for such manufacturing arrangement(s) from the Director of CBER.

Because manufacturing operations conducted at the contract facility will be considered to be under the auspices and utilizing the extended facilities of the licensed establishment, they should be performed under the general supervision and control of the establishment license holder to be eligible for approval. As the license holder, the licensed manufacturer is responsible for maintaining compliance with terms of the license and applicable law at the contracting establishment. Because the contract manufacturer is engaged in the manufacture of a drug, it is also responsible for compliance with applicable provisions of the Food, Drug, and Cosmetic Act as well as regulations applicable to drug manufacturers. Facilities performing contract operations must register with FDA in accordance with registration and listing provisions in part 207. The contract manufacturer should share with the licensed manufacturer all important proposed changes to production as specified in § 601.12 in order for amendments to be filed as necessary under that section.

Contract operations should normally be limited to those operations occurring after the preparation of the final purified concentrate; for example, chemical or biological testing, formulation, sterile filling, lyophilization, or labeling. These operations, while important to the continued purity and potency of the finished product, are not manufacturing processes which by themselves would ordinarily warrant separate

licensing. Contractual arrangements will normally be considered as amendments to the license holder's ELA. However, contract operations which directly affect the product or manufacturing process should also be described in a PLA amendment.

The written request from the licensed manufacturer should include: (1) Signatures of an agreement containing each participating manufacturer; (2) identification of the contract manufacturer and responsible personnel involved in the operation(s) to be performed at the unlicensed facility; (3) a description of the product shipped to the contract manufacturer facility; (4) information describing the manner of shipment of product to and from the contract manufacturer; (5) a description of the operation(s) to be performed at the contract facility; (6) the standard operating procedures to be used applicable to the contract arrangement, including procedures used to segregate biologic production from other manufacturing; (7) a description of the responsibilities of each participant, including the supervision and control exercised by the licensed manufacturer for operations performed at the contract facility; and (8) a commitment from the contract manufacturer facility to inform the licensed manufacture of all important proposed changes in manufacture.

In addition to the written agreement, the licensed manufacturer should submit in its initial or amended establishment license application a description of the contract facility, equipment, and operating procedures; a summary of systems and equipment validation; and documentation of compliance with current good manufacturing practice requirements. Because information concerning operations at the contract site are to be included in the ELA, the license holder should have access to floor plans, equipment validation, and other production information from the contract site necessary to assure purity and potency of the product.

The labeling for end products prepared under a contractual agreement must conform to applicable portions of §§ 610.60 through 610.65. The end product container and package labels should include the name, address, and license number of the licensed manufacturer. Because contract facilities are considered to be an extension of the licensee's establishment, specific identification of the contractor in the product

labeling is not required. The labeling for an intermediate product intended for shipment to a contract facility should include a statement that it is intended for further manufacture.

Dated: November 19, 1992