Guidance for Industry

Cooperative Manufacturing Arrangements for Licensed Biologics

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
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Center for Biologics Evaluation and Research (CBER)
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GUIDANCE FOR INDUSTRY[1]
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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 are capable of performing only limited aspects of manufacturing processes. Consequently, many firms are interested in sharing or contracting parts of manufacturing in order to facilitate product development. Restricting issuance of biological product licenses solely to companies performing all steps in manufacturing could impede the development of new products that involve multiple manufacturers. Therefore, FDA is issuing this guidance to interested persons on cooperative manufacturing arrangements applicable to biological products subject to licensure under section 351 of the U.S. Public Health Service Act (PHS Act). This guidance applies both to products approved with a product (PLA) and associated establishment (ELA) license, and to products subject to a single biologics license application (BLA).

II. INTRODUCTION

Section 351 of the PHS Act (42 U.S.C 262) as amended by the Food and Drug Administration Modernization Act of 1997 on November 21, 1997 (Public Law 105-115), and the regulations promulgated thereunder in 21 CFR 601, provide that a manufacturer may obtain a license to manufacture a biological product on the basis of a demonstration that the biological product that is the subject of the application is safe, pure, and potent. In addition, the facility should meet standards designed to assure that the biological product continues to be safe, pure, and potent. No license may be issued unless the product and establishment meet prescribed requirements and the applicant consents to an inspection of the facility. Such examination is normally conducted during a prelicense inspection. ”Manufacturer” is defined as “any legal person or entity engaged in the manufacture of a product subject to license under the 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 CFR 600.3(t)). “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)).

[1] This guidance has been prepared by the Review Management Coordinating Committee in the Center for Biologics Evaluation and Research. This guidance document represents FDA’s current thinking on Cooperative Manufacturing Arrangements for Licensed Biologics. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

In order to establish adequate control over the manufacturing process for a biological product, to avoid introduction of contaminants during production and to assure lot-to-lot consistency, a manufacturer of a biological product must demonstrate responsibility for and control over the manufacturing process as described in its license application (21 CFR 600.3(t)). Demonstration of adequate supervision and control over the manufacturing of a biological product has often been documented 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 the previous version of this guidance document published in the Federal Register on November 25, 1992 (57 FR 55544), various alternative arrangements involving more than one manufacturer have been accepted. These alternate manufacturing arrangements include short supply and divided manufacturing, as partially described in the current biologics regulations (21 CFR 600.12(e), 601.22, and 610.63), as well as shared and contract manufacturing arrangements.

This revised document describes the Center for Biologics Evaluation and Research's (CBER) current thinking on licensing strategies for meeting the increased need for flexible manufacturing arrangements. Once finalized, this document will supersede "FDA's Policy Statement Concerning Cooperative Manufacturing Arrangements for Licensed Biologics" published in the Federal Register on November 25, 1992. FDA previously published guidance (see Federal Register, July 11, 1995, 60 FR 35750), which clarified that pilot facilities are eligible for licensure provided they are fully qualified and validated, operate in accordance with current good manufacturing practice (cGMP), and otherwise comply with applicable law and regulations. Also, as published in the Federal Register of May 14, 1996 (61 FR 24227), FDA amended regulations in order to eliminate the establishment license application (ELA) requirement for certain specified biotechnology and synthetic biological products subject to licensing under the PHS Act. In the Federal Register of July 31, 1998 (63 FR 40858), FDA proposed to further amend regulations to eliminate references to the PLA and ELA for all products regulated under section 351 of the PHS Act and replace such references with the BLA. The May 14, 1996 rulemaking also amended 21 CFR 600.3(t) to broaden the definition of the term "manufacturer" as it is used in parts 600 through 680. A manufacturer now 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 210, 211, 600 through 680, and 820. This revision of this guidance document addresses the manufacturing arrangements made available by the new definition of manufacturer.

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

III. SHORT SUPPLY ARRANGEMENTS

Under 21 CFR 601.22, a licensed biologic manufacturer may obtain certain materials that 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 21 CFR parts 207 and 607; (3) the licensed product 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 licensed product 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, specific types of human plasma containing rare antibodies, venoms used in producing antitoxins and antivenins, and materials made in non-human animals.

The licensed manufacturer desiring to enter into a short supply agreement should either file the required information and assurances with its initial license application or reported to CBER as a change to an approved application as described in 21 CFR 601.12. Please note that these source material suppliers are subject to FDA inspection.

IV. DIVIDED MANUFACTURING ARRANGEMENTS

Divided manufacturing is an arrangement in which two or more manufacturers, each registered with FDA in accordance with part 207 or 607 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 supplements to the manufacturers' license applications. The supplements should describe the steps to be performed at each facility and the labeling that will be used on any intermediate and final products. Among the factors that FDA intends to assess in determining whether to approve such supplements are conformance to licensed manufacturing procedures and specifications, equivalence of the intermediate products, 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 final product recalls, adverse events, and product complaint reports.

Current biologics regulations prescribe record-keeping requirements for each party in a divided manufacturing arrangement (see 21 CFR parts 210, 211, and 600.12(e)). Other regulations require that the name, address, and license number of each participating licensed manufacturer appear on the package label, and on the label of the container if capable of bearing a full label (see 21 CFR 610.63). With respect to 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. 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 21 CFR 610.63 to be met by placing the name, address, and license number of the manufacturer of the finished dosage form of the biological product on the outer label affixed to the package and by placing the names, addresses, and license number(s) of preceding intermediate product manufacturer(s) 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:

FDA recognizes 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 to not 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 either a shared or contract manufacturing arrangement with one or more manufacturers, as described below.

V. SHARED MANUFACTURING ARRANGEMENTS

Shared manufacturing is an arrangement in which two or more manufacturers are licensed and responsible for specific, different aspects of the manufacture of a product but neither is licensed for all aspects of the product manufacturing. 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. Critical manufacturing steps that may affect the product's safety, purity, or potency and that FDA has considered adequate for separate licensure 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; (6) physical and chemical modifications; (7) required infectious disease testing of blood and blood components; and (8) 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 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 also recognizes that companies may conceive and develop innovative products through extensive preclinical and clinical testing, but choose to limit their participation in product manufacturing. Therefore, FDA intends to also consider eligible for separate licensure a company that is both instrumental in product development and that performs (or is responsible for the performance of) several final manufacturing steps e.g. 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 207 or 607. Each manufacturer should submit a separate BLA or PLA/ELA describing the manufacturing facilities and operations applicable to the preparation of that manufacturer's biological substance or product. Each application should conform to the provisions contained in 21 CFR 601.2 and should fully describe the extent of manufacturing and testing performed by that participating manufacturer, the specifications, the storage and shipping conditions, and the labeling that will accompany that manufacturer's product. Please refer to the appropriate guidance document regarding submission of chemistry, manufacturing, and controls information for technical guidance on the content and format of an application.

All license applications that pertain to a particular product to be manufactured under a shared manufacturing arrangement should be submitted concurrently in order for a complete review of the product to occur, since determining the approvability of the product to be licensed will depend on information contained in all related applications. Lack of one or more related applications may be considered a basis for a refusal to file action per the CBER Refusal to File (RTF) Guidance for Product License Applications (PLAs) and Establishment License Applications (ELAs), dated July 12, 1993.

A common shared manufacturing arrangement is one in which one manufacturer is responsible for an intermediate product and another for the final product. Applications for an intermediate product for further manufacturing use should include, in addition to other information in a license application, the criteria used to determine lot-by-lot acceptability of the product, including sterility (or bioburden), stability, product characterization, potency, and purity specifications. Manufacturers of all intermediate products should demonstrate that their component biological products will consistently meet established specifications. 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 final product. Similarly, FDA intends to accept only those license applications for final products in a shared manufacturing arrangement that specify the source(s) of the licensed intermediate product(s) to be used. The approval of the final product will be dependent upon a demonstration of established specifications for receipt and acceptance of the intermediate(s).

FDA expects the applicant that prepares (or is responsible for the preparation of) the product in final form for commercial distribution to undertake primary responsibility for providing data demonstrating the identity, purity, strength, quality, potency, safety, and efficacy of the final product. In a shared manufacturing arrangement, this applicant 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 also expects the licensed finished product manufacturer to be primarily responsible for any post-approval obligations, such as postmarketing clinical trials, additional product stability studies, complaint handling, recalls, error and accident reporting, and adverse experience reporting.

Each licensed manufacturer in a shared manufacturing arrangement must notify CBER regarding proposed changes in the manufacture, testing, or specifications of its component biological product, in accordance with 21 CFR 601.12 (see two guidance documents entitled “Changes to an Approved

Application: Biological Products" and "Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products" dated July 1997) and also notify the other participating licensed manufacturer(s). All manufacturers participating in a shared manufacturing arrangement must also comply with the record keeping requirements of 21 CFR parts 210, 211, and section 600.12(e).

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

VI. CONTRACT MANUFACTURING ARRANGEMENTS

For the purposes of this document, contract manufacturing refers to a situation in which a license applicant establishes a contract with another entity(ies) to perform some or all of the manufacture of a product as a service to the license applicant. The current definition of "Manufacturer" is any "legal person or entity engaged in the manufacture of a product subject to license under the 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 CFR 600.3 (t)). As described in the Federal Register of May 14, 1996, an applicant who does not own all facilities where significant manufacturing is performed may now apply for licensure of a biological product, either with a single license with a contract manufacturing arrangement or under a shared manufacturing arrangement. Furthermore, a contract facility that is engaged in significant manufacturing is no longer required to be separately licensed.

The license applicant (the manufacturer by definition in 21 CFR 600.3(t)) is responsible for the identity, purity, strength, quality, potency, safety and efficacy of the product and for ensuring that manufacture of the product complies with the provisions of the license application and the applicable regulations including, but not limited to, 21 CFR parts 210, 211, 600 through 680, and 820. Since the license applicant is responsible for compliance with applicable product and establishment standards at all owned and contract facilities, applicants considering contract arrangements are encouraged to verify the FDA inspectional status of the contract facility. Because the contract facility is engaged in the manufacture of a drug or device, it is also responsible for compliance with applicable provisions of the Food, Drug, and Cosmetic Act (FD&C Act) (21 USC 301) and applicable regulations. Facilities performing contract operations for biological products must register with FDA in accordance with registration and listing provisions in 21 CFR part 207, 607, or 807. Because the applicant assumes responsibility for compliance of the contract site with the applicable product and establishment

standards, the applicant should have access to floor plans, equipment validation, and other production information from the contract site necessary to assure safety, purity and potency of the product. The applicant should be fully informed of all deviations, complaints, and adverse events, as well as the results of all tests and investigations regarding or possibly impacting the product. The contract manufacturer should also share with the applicant all important proposed changes to production and facilities (including introduction of new products); the license holder is responsible for reporting, as specified in 21 CFR 601.12, these changes to the FDA (See guidance documents entitled "Changes to an Approved Application: Biological Products" and "Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products" dated July 1997). The responsibilities of each party should be described in written agreements between the license applicant and the contract manufacturer (see below).

The license applicant is responsible for assuring compliance with both product and establishment standards. The product and establishment standards and cGMPs include, but are not limited to, the following:

- safety and effectiveness (identity, purity, strength, quality, potency, safety, efficacy, release and in-process specifications)
- adverse event, error and accident, and product complaint reporting systems
- development and validation of the production process
- reporting changes to the production process as required by 21 CFR 601.12
- quality assurance oversight and change control for master and batch production records
- quality control methodology as it relates to the production process
- submission of protocols and samples for lot release where applicable
- content of the license application
- labeling
- contracts with the establishment(s) at which manufacturing and testing is being performed
- validation, maintenance and proper functioning of all equipment and systems, as well as the facility itself
- environmental and other required monitoring
- reporting changes at all facilities to the FDA, as required in 21 CFR 601.12
- training of personnel

Although the license applicant is responsible for these issues, it is possible that the actual conduct of these steps may be performed by an entity contracted by the license applicant. The license applicant should have established procedures for regularly assessing a contract manufacturing facility's compliance with the applicable product and establishment standards. This may include, but is not limited to, review of all batch records and manufacturing deviations and defects, and periodic audits.

Contract facilities engaged in the manufacture of a biological product are responsible for compliance with applicable provisions of the FD&C Act and will be subject to FDA inspection as provided for in section 351(c) of the PHS Act and section 704(a) of the FD&C Act. The license applicant should ensure that all owned and contract facilities are ready for inspection. The license applicant should obtain assurance from the contractor that any FDA citation of a deviation from cGMP will be shared with the license applicant to allow evaluation of its impact on the purity, potency, and safety of the applicant's product. Information obtained during the inspection of a contract facility may also be disclosed to the license applicant by the FDA in accordance with 21 CFR 200.10. Compliance actions may be taken against both the licensee and the contract manufacturer for failure of the contract manufacturer to comply with cGMP or otherwise fulfill requirements of the license for which the contract manufacturer is responsible.

The applicant's license application (and supplements) should describe all manufacturing, testing, and storage locations, and identify whether they are owned by the applicant or are contract facilities. Please refer to 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 complete description of all contract manufacturing operations. In addition, for each contract arrangement, the applicant's license application should describe the product subject to contract manufacturing including: (1) the product stability and the manner of shipment to and from the contract facility, (2) the responsibilities of each participating entity, and (3) 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 applicant may want to consider a shared manufacturing arrangement. Cross referencing of master files should be limited to circumstances involving proprietary information, such as a list of all products manufactured in a contract facility (in this situation the applicant should be kept informed of the types or categories of all products manufactured in the contract facility) and non-compendial test procedures (SOPs) (provided there is assurance that both the applicant and FDA will be informed of all changes in these procedures). The license application(s) may also refer to Master Files for information regarding containers and closures.

FDA recommends that applicants entering into a contract arrangement, have a signed, written agreement with the contractor regarding the following:

- identification of the contract manufacturer and the locations to be used for manufacture of the applicant's product
- a description of the responsibilities of each participant, including the quality assurance function of the contractor and the supervision and control exercised by the license applicant

- a description of the product shipped to the contract facility
- information describing the manner and conditions of shipment of product to and from the contract facility
- a description of the operation(s) to be performed at the contract facility
- the standard operating procedures to be used applicable to the contract arrangement, including procedures used to segregate manufacturing of different products
- a commitment from the contract facility to inform the license applicant of all proposed changes in manufacture and facilities prior to implementation, including introduction of additional marketed products and clinical material processing operations
- a commitment from the contract facility to fully inform the license applicant of all errors and deviations in manufacturing methods and test results, as well as adverse events, for the affected product
- a description of how and when the contract facility will be periodically assessed by the license applicant for compliance with applicable product and establishment standards and cGMP.

The labeling for final products prepared under a contractual agreement must conform to applicable portions of 21 CFR 610.60 through 610.65. The final product container and package labels should include the name, address, and license number of the license applicant. Because the contract facilities are considered to be under the auspices of the license holder, specific identification of the contractor in the product labeling is not required. The labeling for an intermediate product intended for shipment to or from a contract facility should include a statement that it is intended for further manufacture and should not bear a U.S. license number.

VII. REFERENCES

1. FDA's Policy Statement Concerning Cooperative Manufacturing Arrangements for Licensed Biologics, November 25, 1992, Federal Register, Vol. 57, p. 55544.
2. FDA Guidance Document Concerning Use of Pilot Manufacturing Facilities for the Development and Manufacture of Biological Products, July 11, 1995, Federal Register, Vol. 60, p. 35750.
3. Elimination of Establishment License Application for Specified Biotechnology and Specified Synthetic Biological Products, Final Rule, May 14, 1996, Federal Register, Vol. 61, p. 24227.
4. CBER Refusal to File (RTF) Guidance for Product License Applications (PLAs) and Establishment License Applications (ELAs), dated July 12, 1993.
5. Guidance for Industry: Changes to an Approved Application: Biological Products - 7/97.

6. Guidance for Industry: Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products – 7/97

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" - 5/99 -

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 - 4/99

9. Guidance for Industry: Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Biological In Vitro Diagnostic Product - 3/99

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 - 2/99

11. Guidance for Industry: Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Vaccine or Related Product - 1/99

12. Guidance for Industry: for the Submission of Chemistry, Manufacturing, and Controls Information for Synthetic Peptide Substance - 1/98

13. Guidance For the Submission of Chemistry, Manufacturing and Controls Information and Establishment Description for Autologous Somatic Cell Therapy Products - 1/97

14. 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 - 8/96