(regardless of the scale of manufacture) which is fully qualified, validated, operates in accordance with current good manufacturing practices (CGMP's), and otherwise complies with applicable law and regulations. In order to further streamline the approval process, the agency is currently considering changing its procedures to eliminate the requirement for a separate establishment license for certain well defined classes of biologic products. Because of recent scientific advances, both in methods of manufacture and in methods of analysis, some products developed through biotechnology can be characterized in ways not historically considered possible. Thus, the agency is considering allowing ''biotech'' products that are well characterized to be regulated under a single application. The agency plans to hold a scientific conference in the fall of 1995, to develop a definition of well characterized products that may be amenable to regulation under new procedures.

This guidance document describes the conditions and procedures for submitting establishment license applications (ELA's) for pilot facilities and for subsequent transfer of product manufacturing to a different facility. The guidance document provides information concerning: (1) Use of a product manufactured in a pilot facility in clinical trials conducted to demonstrate safety and effectiveness and optional transition to a different facility; (2) submissions for approval to use a pilot facility for manufacture of a product; (3) submissions for approval to use a different manufacturing facility while a product license application (PLA) for a product manufactured in a pilot facility and an ELA for a pilot facility are pending; (4) submissions for approval to use a different manufacturing facility when a product and pilot facility are currently licensed; and (5) submission of a PLA based on data obtained from a product made in a pilot facility when licensure of the product manufactured in the pilot facility and of the pilot facility is not sought.

The guidance also addresses review timeframes and submission times, product consistency, data comparing products made in different facilities, and product availability at the time of product licensure.

In addition, FDA intends to revise the policy statement entitled ''Manufacturing Arrangements for Licensed Biologics'' published in the **Federal Register** of November 25, 1992 (57 FR 55544) to accommodate these procedures.

This guidance document is not binding on either FDA or manufacturers of biological products and does not create or confer any rights, privileges, or benefits for or on any person.

Interested persons may submit to the Dockets Management Branch (address above) written comments on the guidance document. Received comments will be considered to determine if further revision to the guidance document is necessary.

The title and text of the guidance document follows:

Center for Biologics Evaluation and Research; Use of Pilot Manufacturing Facilities for the Development and Manufacture of Biological Products; Guidance

I. Introduction

Biological products, which generally include vaccines, blood and blood products, allergenic extracts, and biological therapeutics, are regulated under section 351 of the Public Health Service Act (the PHS Act) (42 U.S.C. 262), as well as the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321). The PHS Act requires that biological products be propagated or manufactured and prepared at an establishment holding an unsuspended and unrevoked license. Lack of clarity about licensing requirements has led some applicants to make major investments in large scale manufacturing facilities before initiating the clinical trial(s) necessary to demonstrate the safety and effectiveness of their products. Such investments can result in significant financial loss if the product is not ultimately brought to market. In this document, the Center for Biologics Evaluation and Research (CBER) is providing guidance to manufacturers and developers of biological products to clarify licensing procedures for the use of pilot facilities for the manufacture of biological products. CBER considers a pilot production to be a procedure and facility fully representative of and simulating that to be applied on a full commercial scale. For example, the methods of cell expansion, harvest, and product purification should be identical except for scale of production. These facilities are sometimes collectively referred to by industry as ''pilot facilities'' and will be referred to as ''pilot'' in this document. These facilities are to be distinguished from facilities used in research and development that may not operate under appropriate current good manufacturing practices (CGMP's).

II. Background

CBER recognizes that development of important new biological products may be expensive and time consuming and that companies must be able to forecast and evaluate their expenditures for this process. Constructing a large scale facility to manufacture a product that has not been fully tested in clinical trials could result in a major capital loss if delays occur or the product is not ultimately brought to market. CBER also recognizes that for some companies, the best financial option may be the use of a pilot facility where a product may be manufactured at a smaller scale than might be eventually desired for an approved product. While CBER has not objected to the use of pilot facilities for the manufacture of clinical material (provided such manufacture is in compliance with requirements applicable to investigational drugs), many companies are concerned that these facilities and the product manufactured in them would not be eligible for licensure. An application for establishment licensure can be made for any facility (regardless of the scale of manufacture) that has been fully qualified and validated, that operates under CGMP's, and that otherwise complies with applicable laws and regulations. This guidance document describes the conditions and procedures for submitting such application(s) and for subsequent, optional transfer of product manufacturing to a different manufacturing facility.

III. Guidance

The following provides information on the submission of product license applications (PLA's) and establishment license applications (ELA's) and investigational new drug applications (IND's) for products manufactured in a pilot facility.

1. Use of a product manufactured in a pilot facility in clinical trials conducted to demonstrate safety and effectiveness and optional transition to a different facility.

IND's for all products should include information that describes where the material for the clinical trial(s) used to demonstrate safety and effectiveness is or was manufactured. Data submitted in support of licensure of a biological product can be obtained using a product manufactured in a pilot facility. In the event that a product manufactured in new facilities and/or scaled-up processes or facilities is intended to be used at a later date for either completion of the clinical trial(s) demonstrating safety or effectiveness or for licensable product, the time tables, new locations, and processes should be identified in the IND. A protocol for comparing products should also be submitted. Data which compares a product made in a new facility or with new processes to a product used in earlier clinical studies should be submitted to the IND before including the new product in the clinical trial(s). If the product made in the new facility or by the new process will not be used in the clinical trials used to demonstrate safety or effectiveness, the data comparing the two products should be submitted in the IND, PLA, or PLA supplement. A description of any manufacturing changes that were made as a result of using a new facility or new processes and stability data should also be submitted to the IND or PLA as appropriate.

2. Submissions for approval to use a pilot facility for manufacture of a product.

Information and data submitted in the PLA should be obtained using a product manufactured in the pilot facility. The ELA should include a completed Form FDA 3210; Application for Establishment License for Manufacture of Biological Products (FDA