contact: Michael Beatrice, Center for Biologics Evaluation and Research (HFM–10), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448, 301–496–3556.

SUPPLEMENTARY INFORMATION: FDA believes that the practice of submitting an incomplete or inadequate application and later "repairing" it during an extended review period is inefficient and that it wastes agency resources. Accepting an application that is obviously in need of extensive modification is unfair to those sponsors who have fulfilled their scientific and legal obligations by submitting a complete and fully analyzed application. An incomplete application, submitted prematurely, may delay review of a more complete application from another sponsor. Moreover, an incomplete or inadequate application that needs several cycles of FDA response and sponsor repair excessively consumes FDA and industry resources. The incomplete or inadequate application generates more "start-up time" as well as extra reviews, letters, and meetings.

FDA's regulations describe certain circumstances in which the agency may refuse to file an application (§§ 314.101 and 601.2 (21 CFR 314.101 and 601.2)). Both CDER and CBER have decided that a more detailed explanation of how they are implementing these regulations can improve substantially the efficiency of their review processes. Because of the differences in the CDER and CBER regulations and programs, separate but similar guidance documents have been developed.

CDER's regulations describe in some detail when CDER will refuse to file an application. Section 314.101(d)(3), states: "The application or abbreviated application is incomplete because it does not on its face contain information required under section 505(b) and section 505(j), or section 507 of the act and § 314.50 or § 314.94." CDER's guidance document clarifies the manner in which FDA is applying § 314.101(d)(3). RTF decisions may also be made under other provisions of § 314.101 (i.e., those provisions included in § 314.101(d)(1), (d)(2), (d)(4) through (d)(9), and (e)), but are not specifically addressed in the guidance document.

CBER's regulations list general categories of information required to be submitted in any establishment or product license application. CBER's guidance document describes how CBER makes threshold determinations that the information submitted to support licensure is sufficiently complete to permit a substantive and meaningful review.

Both guidance documents recognize that although RTF is not a final determination and is often an early opportunity for the sponsor to develop a reviewable and potentially approvable application, it is a significant step that delays, at least for a time, full review of the application. Therefore, it is important that RTF be reserved for applications with defects that make the application plainly inadequate or nonreviewable plainly without major repair, or that make review unreasonably difficult. Both guidance documents indicate that in general the deficiencies leading to RTF should be objective and straightforward, not matters of subtle judgment, and should not be quickly reparable.

FDA has concluded that explaining how it applies its regulations in making RTF decisions will substantially improve the quality of NDA, PLA, and ELA submissions and the efficiency of the new drug evaluation and biological product review processes.

To assess the scientific and procedural quality of RTF decisions, CDER recently announced the formation of a committee to review RTF decisions (58 FR 28983, May 18, 1993). The CDER RTF review committee consists of senior CDER and CBER officials, and FDA's Chief Mediator and Ombudsman. The review committee will examine selected CDER RTF's to assess, among other things: The consistency of RTF practices throughout new drug evaluation offices and divisions, the need for additional guidance on application content and format, and the need to modify CDER's RTF policies. CBER will develop a similar oversight mechanism in which CDER will be represented. The presence of CBER representatives on CDER's review committee and the participation of CDER representatives in CBER's oversight process will help to ensure consistent application of RTF principles throughout the Centers.

Interested persons may, on or before September 20, 1993, submit to the Dockets Management Branch (address above) written comments on the guidance documents. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: July 14, 1993.

Michael R. Taylor,

Deputy Commissioner for Policy.

[FR Doc. 93–17088 Filed 7–16–93; 8:45 am]

BILLING CODE 4160–01–F

[Docket No. 93N–0202]

Guidance on Alternatives to Lot Release for Licensed Biological Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is describing its current practices governing lot release for licensed biological products. This document describes the information that should be submitted by manufacturers of licensed biological products and the approach that FDA's Center for Biologics Evaluation and Research (CBER) is using when evaluating alternatives to lot release. CBER's decisions in this regard are based on a continued assurance that the safety, purity, and potency of the product will be maintained. This action is being taken in response to requests for guidance on alternatives to lot release. FDA invites comments on this guidance statement.

DATES: Submit written comments by September 20, 1993.

ADDRESSES: Submit written comments and information to the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857. Submit product license application amendments requesting alternatives to lot release and sample submission requirements to the director of the application division within the office having primary jurisdiction over the product (e.g., Office of Therapeutics, Office of Vaccines, or Office of Blood), Food and Drug Administration, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Rockville, MD 20852–1448.

FOR FURTHER INFORMATION CONTACT: JoAnn M. Minor, Center for Biologics Evaluation and Research (HFM–635), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448, 301-295-9074.

SUPPLEMENTARY INFORMATION: FDA is describing its current procedure for considering requests from manufacturers regarding alternatives to the submission of samples and of protocols that show results of applicable tests (commonly called "lot release") as set forth in 21 CFR 610.2. This notice

also responds to requests for guidance on what information should be provided when submitting such requests.

Introduction

Under section 351(d) of the Public Health Service Act (42 U.S.C. 262(d)) an establishment may be issued a license to manufacture a biological product only after showing that the establishment and product meet standards designed to ensure that product's continued safety, purity, and potency. Thereafter, a manufacturer of a biological product subject to a license must demonstrate supervision and control of the entire manufacturing process to ensure, among other things, that contaminants are not introduced during production and that there is lot-to-lot consistency in the quality of the licensed product (see 21 CFR part 600 *et seq.*).

Under § 610.2, manufacturers may be required to submit samples from all lots of a licensed biological product together with the protocols showing results of applicable tests when deemed necessary by the Director, CBER. For most biological products, CBER has required the submission of this information both in support of a license application and for continued lot release following product license application approval. In these instances, a manufacturer may not distribute any product until the Director, CBER, issues an official release for the lot.

Guidance and Rationale

Biological products historically have been primarily complex mixtures produced by living organisms. The products have ranged from whole blood for transfusion to allergenic extracts, vaccines, and recombinant therapeutics. Current technology enables industrial scale production of biological products which are more easily characterized using reproducible methodology. In addition, improved analytical techniques are available for characterization of starting materials as well as final products, and efficient methods of purification can reduce levels of process-related impurities to a minimum.

Current technology combined with the experience derived from years of product-specific inspections and testing in CBER laboratories has demonstrated that, for some biological products, alternatives to requiring a CBER release action for every lot provide adequate control to ensure continued safety, purity, and potency (including effectiveness). Therefore, manufacturers meeting the assurances described in this document may submit product license application amendments requesting approval of alternatives to the lot release requirements set forth in their license. Such product license application amendments may be submitted once a manufacturer has documented an acceptable history of lot release and control of the manufacturing facility. The definition of acceptable lot release history will vary according to the product and the complexities of the manufacturing process. CBER considers granting requests for alternatives to lot release only upon demonstration that the alternative approach does not compromise the safety, purity, and potency of the biological product. Specific questions should be addressed to the office with product responsibility prior to submission of an amendment requesting alternatives to lot release.

Among the factors that CBER assesses in determining whether to approve such amendment requests are conformance to licensed manufacturing procedures and the ability of the manufacturer to consistently demonstrate product safety, purity, potency, and stability.

In addition, there should be a history of FDA establishment inspections that have shown compliance with applicable regulations during the period covered. The period considered may vary by product, because the number of lots produced in a given time may vary, as may the extent to which lot release procedures are viewed as important for ongoing assurance of safety and efficacy. CBER recognizes that the need for submission of lot release protocols and/or samples may be greater for some products than others, e.g., products where maintenance of consistent specifications from lot-to-lot is difficult and/or where insufficient correlation is available between measurement of potency and biological activity. The experience reflected in both the number of lots produced and the period of production is important to assess the potential value of the lot release procedures for a particular product or product class.

The following data should be submitted in the form of a product license application amendment covering an adequate period of time and a sufficient number of product lots:

(1) A well-organized table containing a testing summary of all lots manufactured, including lots manufactured in support of licensure. This testing history should include both lots submitted to CBER for release action and lots or batches rejected during in-process, bulk, or final testing at the manufacturing establishment.

(2) A summary of the disposition of the above lots, including the reason a final lot was not submitted to CBER for release or an in-process, or bulk lot or batch was rejected.

(3) A summary listing of all product complaints which include, but are not limited to, presence of labeling errors, decreased potency, contamination, particulate matter, adverse reactions, and defect reports. The actions taken by the manufacturer for each identified production lot or batch should be described.

(4) A listing of any lot(s) which was subject to recall or market corrective action following distribution.

(5) A description of any major process change, including when the process change was implemented and a list of lots manufactured using the new procedure.

After evaluating a license amendment requesting permission to use alternatives to lot release, CBER may determine that routine submission of lot release protocols and samples is not necessary if the submission describes alternatives which provide continued assurance of safety, purity, and potency. CBER may consider whether there is a need for manufacturers to submit samples and protocols at specific intervals (e.g., quarterly) for surveillance purposes. Such lots should be randomly selected in each period, or as instructed by the Director, CBER. Regardless of CBER's determination on submitting lot release protocols and/or samples, the manufacturer is required to maintain sufficient records, retention samples and stability test samples as required by 21 CFR 211.170 and 211.180.

The approach described above is based upon a retrospective analysis of lot release history at CBER, including a comparison of the number of lot failures to the total number of lots tested. Where a major change in manufacturing process or establishment is proposed or has occurred which requires an amendment, CBER may consider reimposing the requirement for submission of lots for release in addition to lots submitted in support of the amendment. Furthermore, if a product surveillance sample is tested and fails a required test or established specification, the product may be subject to recall by the manufacturer and/or the requirement for lot release may be reimposed.

CBER is currently applying the approach set forth in this notice. This notice provides information about, but does not set forth specific requirements for, the submission of a product license amendment requesting permission to use alternatives to lot release. FDA does not intend for this guidance to be comprehensive. All information in this

guidance may not be applicable to all situations.

This notice is intended as guidance to manufacturers of biological products filing product license amendments to request alternatives to lot release. If a manufacturer believes that the factors described in this guidance are inapplicable to a particular product and other factors are appropriate for CBER's consideration, the manufacturer may wish to discuss the matter further with the agency to prevent expenditure of money and effort on activities that later may 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 upon any person, manufacturer, or organization.

Interested persons may, on or before September 20, 1993 submit to the Dockets Management Branch (address above) written comments and information on this guidance statement. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments and information should be identified with the docket number found in brackets in the heading of this document. The notice and received information and comments are available for public examination in the office above between 9 a.m. and 4 p.m., Monday through Friday.

FDA will consider any comments received in determining whether amendments to the guidance statement are warranted. As warranted, FDA will announce the availability of any revised guidance statement in the **Federal Register**.

Dated: July 14, 1993.

Michael R. Taylor,

Deputy Commissioner for Policy.

[FR Doc. 93–17133 Filed 7–19–93; 8:45 am]

BILLING CODE 4160–01–F

Advisory Committees; Notice of Meetings

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: This notice announces forthcoming meetings of public advisory committees of the Food and Drug Administration (FDA). This notice also summarizes the procedures for the meetings and methods by which interested persons may participate in open public hearings before FDA's advisory committees.

MEETINGS: The following advisory committee meetings are announced:

Circulatory System Devices Panel of the Medical Devices Advisory Committee

Date, time, and place. August 2 and 3, 1993, 8:30 a.m., Bethesda Ramada Inn, Embassy Ballroom, 8400 Wisconsin Ave., Bethesda, MD.

Type of meeting and contact person. Open public hearing, August 2, 1993, 8:30 a.m. to 9:30 a.m., unless public participation does not last that long; open committee discussion, 9:30 a.m. to 3 p.m.; closed presentation of data, 3 p.m. to 4 p.m.; open public hearing, August 3, 1993, 8:30 a.m. to 9:30 a.m., unless public participation does not last that long; open committee discussion, 9:30 a.m. to 3 p.m.; closed presentation of data, 3 p.m. to 4 p.m.; Wolf Sapirstein or Ramiah Subramanian, Center for Devices and Radiological Health (HFZ–450), Food and Drug Administration, 1390 Piccard Dr., Rockville, MD 20850, 301–427–1205.

General function of the committee. The committee reviews and evaluates data on the safety and effectiveness of marketed and investigational devices and makes recommendations for their regulation.

Agenda—Open public hearing. Interested persons may present data, information, or views, orally or in writing, on issues pending before the committee. Those desiring to make formal presentations should notify the contact person before July 23, 1993, and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, and an indication of the approximate time required to make their comments.

Open committee discussion. The committee will discuss one or more premarket approval applications for implantable cardioverter defibrillator devices and an interventional cardiology device.

Closed presentation of data. The committee may discuss trade secret and/or confidential commercial information regarding the devices listed above. This portion of the meeting will be closed to permit discussion of this information (5 U.S.C. 552b(c)(4)).

Dental Products Panel of the Medical Devices Advisory Committee

Date, time, and place. August 2 and 3, 1993, 8 a.m., Parklawn Bldg., conference rms. D and E, 5600 Fishers Lane, Rockville, MD.

Type of meeting and contact person. Open committee discussion, August 2, 1993, 8 a.m. to 4 p.m.; closed committee deliberations, 4 p.m. to 5 p.m.; open public hearing, August 3, 1993, 8 a.m. to 4 p.m., unless public participation does not last that long; closed committee deliberations, 4 p.m. to 4:30 p.m.; Jeanne L. Rippere, Center for Drug Evaluation and Research (HFD–813), Food and Drug Administration, 7520 Standish Pl., Rockville, MD 20855, 301–295–8186.

General function of the committee. The committee reviews and evaluates data on the safety and effectiveness of marketed and investigational devices and makes recommendations for their regulation.

Agenda—Open public hearing. Interested persons may present data, information, or views, orally or in writing, on the general issues pending before the committee. Those desiring to make formal presentations should notify the contact person before July 28, 1993, and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, and an indication of the approximate time required to make their comments.

Open committee discussion. The committee will hear and discuss orientation presentations on the role of the committee and its plaque subcommittee in the review and evaluation of safety and effectiveness data for over-the-counter (OTC) drug products bearing antiplaque and antiplaque-related claims, such as "for the reduction or prevention of plaque, tartar, calculus, film, sticky deposits, bacterial build-up, and gingivitis." These data were submitted in response to a call-for-data notice published in the **Federal Register** of September 19, 1990 (55 FR 38560). In addition, the committee will hear short presentations on issues that will be discussed at length at the next Panel meeting, tentatively scheduled for December 1 through 3, 1993. These issues include the regulation of dental amalgam and dental product labeling requirements.

Closed committee deliberations. The committee may discuss trade secret and/or confidential commercial information related to OTC drug products for plaque reduction and/or prevention. This portion of the meeting will be closed to permit discussion of this information (5 U.S.C. 552b(c)(4)).

Drug Abuse Advisory Committee

Date, time, and place. August 25, 1993, 9 a.m., Holiday Inn, Plaza Ballroom, 8777 Georgia Ave., Silver Spring, MD.

Type of meeting and contact person. Open public hearing, 9 a.m. to 10 a.m., unless public participation does not last