of its regulatory process. FDA's regulations in part 25 (21 CFR part 25) specify that EA's or abbreviated environmental assessments (AEA's) must be submitted as part of certain NDA's, antibiotic applications, ANDA's, AADA's, IND's, and for other various actions. This guidance provides information on how to prepare EA's for submission to CDER for these drug product applications. Topics covered in this guidance include: (1) When categorical exclusions apply, (2) when to submit an EA or AEA, (3) the content and format of EA's or AEA's, (4) approaches to determining the environmental fate and effects of substances, (5) test methods, (6) treatment of confidential information submitted in support of an EA, (7) special considerations associated with EA's for genetically altered organisms and materials and products derived from natural sources, (8) EA documentation for foreign manufacturing facilities, and (9) drug master files.

CDER encourages industry to implement the use of the content and format described in this guidance as soon as possible because standardized documentation submitted by industry increases the efficiency and speed of the review process. Alternative content and format styles may be used as long as the regulatory requirements defined in part 25 are satisfied.

Section III.D.7.c of this guidance describes specific circumstances (identified as Tier 0) under which format items 7, 8, 9, 10, 11, and 15 are unnecessary and may be omitted from certain environmental assessments submitted pursuant to § 25.31a(a). Because approval of a product under these circumstances is unlikely to have a significant environmental effect, submission of information for these format items will not ordinarily assist CDER in determining whether an action significantly affects the environment. Therefore, for applications already submitted in which these circumstances exist, the applicant has the option to withdraw the information submitted in format items 7, 8, 9, 10, 11, and 15; and CDER will not review it. The applicant should submit an amendment to the application stating that the circumstances described in Tier 0 exist in the application, and the information is being withdrawn for format items 7, 8, 9, 10, 11, and 15. Because CDER is required to make the EA and a finding of no significant impact (FONSI) publicly available, the applicant should provide, along with the letter, a revised EA with the information in those format items deleted. The applicant should certify that the remaining information has not been revised from what was previously submitted. To avoid unnecessarily complicating the review process if the review has already been completed, the applicant should state in the letter that it waives the request to withdraw this information if CDER has prepared a FONSI based on the previously submitted information. CDER requests that pending applications be amended on or before February 12, 1996. A copy of the amendment cover letter should be sent to the contact person (address above). The applicant has the option of checking with the contact person regarding the status of the environmental review for its pending application. An amendment of this type will not affect the user fee due date required by the Prescription Drug User Fee Act of 1992 (Pub. L. 102–571).

Under the President's reinventing government (REGO) initiatives announced in April 1995, CDER is reevaluating its environmental regulations and plans to reduce the number of EA's required to be submitted by industry and, consequently, the number of FONSI's prepared by the agency under NEPA. FDA will publish in a future issue of the Federal Register a proposed rule concerning proposed additional categorical exclusions for those actions CDER has determined normally do not individually or cumulatively have a significant effect on the quality of the human environment. This guidance explaining how to prepare an EA when required by current regulations will remain in effect until superseded by revised final regulations or new CDER guidance.

Although this guidance does not create or confer any rights, for or on any person, and does not operate to bind FDA, it does represent the agency's current thinking on how to prepare environmental assessments for submission to CDER.

Interested persons may, at any time, submit to the Dockets Management Branch (address above) written comments on the guidance. 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 brackets in the heading of this document. The guidance and received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: January 2, 1996.

William B. Schultz,

Deputy Commissioner for Policy.

[FR Doc. 96–420 Filed 1–10–96; 8:45 am]

BILLING CODE 4160–01–F

Investigational Biological Product Trials; Procedure to Monitor Clinical Hold Process; Meeting of Review Committee and Request for Submissions

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing a meeting of the clinical hold review committee, which reviews the clinical holds that the Center for Biologics Evaluation and Research (CBER) has placed on certain investigational biological product trials. CBER held its first clinical hold review meeting on May 17, 1995. FDA is inviting any interested biological product company to use this confidential mechanism to submit to the committee for its review the name and number of any investigational biological product trial placed on clinical hold during the past 12 months that the company wants the committee to review.

DATES: The meeting will be held in February 1996. Biological product companies may submit review requests for the February meeting by January 30, 1996.

ADDRESSES: Submit clinical hold review requests to Amanda B. Pedersen, FDA Chief Mediator and Ombudsman, Office of the Commissioner (HF–7), Food and Drug Administration, rm. 14–105, 5600 Fishers Lane, Rockville, MD 20857, 301–827–3390.

FOR FURTHER INFORMATION CONTACT: Joy A. Cavagnaro, Center for Biologics Evaluation and Research (HFM–2), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448, 301–827–0379.

SUPPLEMENTARY INFORMATION: FDA regulations in part 312 (21 CFR part 312) provide procedures that govern the use of investigational new drugs and biologics in human subjects. These regulations require that the sponsor of a clinical investigation submit an investigational new drug application (IND) to FDA outlining the proposed use of the investigational product. The IND must contain the study protocol, a summary of human and animal experience with the product, and information on the product's characterization, chemistry, pharmacology, and toxicology. FDA reviews an IND to help ensure the safety and rights of human subjects of research and to help ensure that the quality of any scientific evaluation of a drug is adequate to permit an evaluation of the product's efficacy and safety.

If FDA determines that a proposed or ongoing study may pose significant risks for human subjects or is otherwise seriously deficient, as discussed in the investigational new drug regulations, it may impose a clinical hold on the study. The clinical hold is one of FDA's primary mechanisms for protecting subjects who are involved in investigational new drug or biologic trials. A clinical hold is an order that FDA issues to a sponsor to delay a proposed investigation or to suspend an ongoing investigation. The clinical hold may be placed on one or more of the investigations covered by an IND. When a proposed study is placed on clinical hold, subjects may not be given the investigational drug or biologic as part of that study. When an ongoing study is placed on clinical hold, no new subjects may be recruited to the study and placed on the investigational drug or biologic, and patients already in the study should stop receiving therapy involving the investigational drug or biologic unless FDA specifically permits it.

FDA regulations in § 312.42 describe the grounds for the imposition of a clinical hold. When FDA concludes that there is a deficiency in a proposed or ongoing clinical trial that may be grounds for the imposition of a clinical hold order, ordinarily FDA will attempt to resolve the matter through informal discussions with the sponsor. If that attempt is unsuccessful, the agency may order a clinical hold.

A clinical hold is ordered by or on behalf of the director of the division that is responsible for review of the IND. The order identifies the studies under the IND to which the clinical hold applies and explains the basis for the action. The clinical hold order may be made by telephone or other means of rapid communication, or in writing. Following notification of the clinical hold by telephone or other means of rapid communication, CBER promptly provides the sponsor with a written explanation of the basis for the clinical hold.

The clinical hold order specifies whether the sponsor may resume the affected investigation without prior notification by FDA once the deficiency has been corrected. If the order does not permit the resumption without notification, an investigation may resume only after the division director or his or her designee has notified the sponsor that the investigation may proceed. Resumption may be authorized by telephone or other means of rapid communication. If all investigations covered by an IND remain on clinical hold for 1 year or longer, FDA may place the IND on inactive status.

FDA regulations in § 312.48 provide dispute resolution mechanisms through which sponsors may request reconsideration of clinical hold orders. The regulations encourage the sponsor to attempt to resolve disputes directly with the review staff responsible for the review of the IND. If necessary, the sponsor may request a meeting with the review staff and management to discuss the clinical hold.

Over the years, drug sponsors have expressed a number of concerns about the clinical hold process, including concerns about the scientific and procedural adequacy of some agency actions. FDA undertook several initiatives to evaluate the consistency and fairness of the Center for Drug Evaluation and Research's (CDER's) practices in imposing clinical holds. First, CDER completed a centerwide review of clinical holds recorded in their management information system. While some differences in practice and procedure were discerned among divisions in CDER, it appeared that the procedures specified in the regulations were, in general, being followed, and that clinical holds were scientifically supportable. Second, FDA established a committee in CDER to review selected clinical holds for scientific and procedural quality. The committee held pilot meetings in 1991 and met quarterly through 1992. The committee currently meets semiannually as a regular program.

CBER began a similar process to evaluate the consistency and fairness of CBER's practices in imposing clinical holds by instituting a review committee to review clinical holds. CBER also plans to conduct further quality assurance oversight of the IND process. CBER held its first clinical hold review committee meeting on May 17, 1995, and intends to make the clinical hold review process a regular, ongoing program. The committee last met in October 1995. The review procedure of the committee is designed to afford an opportunity for a sponsor who does not wish to seek formal reconsideration of a pending clinical hold to have that clinical hold considered ''anonymously.'' The committee consists of senior managers of CBER, a senior official from CDER, and the FDA Chief Mediator and Ombudsman.

Clinical holds to be reviewed will be chosen randomly. In addition, the committee will review clinical holds proposed for review by biological product sponsors. In general, a biological product sponsor should consider requesting review when it disagrees with the agency's scientific or procedural basis for the decision.

Requests for committee review of a clinical hold should be submitted to the FDA Chief Mediator and Ombudsman, who is responsible for selecting clinical holds for review. The committee and CBER staff, with the exception of the FDA Chief Mediator and Ombudsman, are never advised, either in the review process or thereafter, which of the clinical holds were randomly chosen and which were submitted by sponsors. The committee will evaluate the selected clinical holds for scientific content and consistency with agency regulations and CBER policy.

The meetings of the review committee are closed to the public because committee discussions deal with confidential commercial information. Summaries of the committee deliberations, excluding confidential commercial information, may be requested in writing from the Freedom of Information Office (HFI–35), Food and Drug Administration, rm. 12A–16, 5600 Fishers Lane, Rockville, MD 20857, approximately 15 working days after the meeting, at a cost of 10 cents per page. If the status of a clinical hold changes following the committee's review, the appropriate division will notify the sponsor.

FDA invites biological product companies to submit to the FDA Chief Mediator and Ombudsman the name and IND number of any investigational biological product trial that was placed on clinical hold during the past 12 months that they want the committee to review at its February 1995 meeting. Submissions should be made by January 30, 1996, to Amanda B. Pedersen, FDA Chief Mediator and Ombudsman (address above).

Dated: January 4, 1996.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

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