Dated: November 17, 1999.

William K. Hubbard,

Senior Associate Commissioner for Policy, Planning, and Legislation.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 97D–0318]

Guidance for Industry: Revised Precautionary Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and New Variant Creutzfeldt-Jakob Disease (nvCJD) by Blood and Blood Products; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a guidance document (dated November 1999) entitled ''Guidance for Industry: Revised Precautionary Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and New Variant Creutzfeldt-Jakob Disease (nvCJD) by Blood and Blood Products.'' The guidance document provides comprehensive current recommendations, including new recommendations concerning nvCJD, to all registered blood and plasma establishments and all establishments engaged in manufacturing plasma derivatives. The guidance document is intended to replace the FDA guidance entitled ''Revised Precautionary Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) by Blood and Blood Products,'' dated August 1999.

DATES: Written comments may be submitted at any time. The guidance is released for immediate implementation. For the purposes of this guidance document, FDA interprets immediate implementation to mean as soon as feasible, but not later than April 17, 2000.

ADDRESSES: Submit written requests for single copies of the guidance document entitled ''Guidance for Industry: Revised Precautionary Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and New Variant Creutzfeldt-Jakob Disease (nvCJD) by Blood and Blood Products'' to the Office of Communication, Training, and Manufacturers Assistance (HFM–40), Center for Biologics Evaluation and Research (CBER), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448. Send one self-addressed adhesive label to assist that office in processing your requests. The guidance document may also be obtained by mail by calling the CBER Voice Information System at 1–800–835-–4709 or 301–827–1800, or by fax by calling the FAX Information System at 1–888–CBER–FAX or 3019827–3844. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the guidance document. Submit written comments on the guidance document to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Valerie A. Butler, Center for Biologics Evaluation and Research (HFM–17), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448, 301–827–6210.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a guidance document entitled ''Guidance for Industry: Revised Precautionary Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and New Variant Creutzfeldt-Jakob Disease (nvCJD) by Blood and Blood Products.'' This guidance document is intended to replace the FDA guidance entitled ''Revised Precautionary Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) by Blood and Blood Products'' dated August 1999 (64 FR 44739, August 17, 1999). The guidance document provides comprehensive current recommendations, including new recommendations concerning nvCJD, to all registered blood and plasma establishments and all establishments engaged in manufacturing plasma derivatives.

FDA issued the August 1999 guidance for immediate implementation, and the agency requested that comments on the guidance document be submitted within 60 days of the notice of availability that published in the **Federal Register** announcing the guidance document. After reviewing the comments received, FDA has revised the August 1999 guidance document by issuing this guidance document. Significant changes made to the August 1999 draft guidance document since the 60-day comment period closed are as follows:

(1) A new recommended deferral for donors who have injected bovine insulin since 1980 unless it has been established that the product was not manufactured since 1980 from cattle in the United Kingdom;

(2) Removal of the deferral for recipients of human-pituitary derived gonadotropins;

(3) A change in the suggested question to exclude donors with dura mater transplants;

(4) In the case of travel to the United Kingdom, a change in the recommended frequency for donor questioning, now specified to take place only once for the donor;

(5) An exception to consignee notification for the purpose of retrieval, quarantine, and destruction of blood components if there is definite knowledge that the plasma given to a consignee will no longer exist in the form of unpooled units; and

(6) Additional clarification with regard to recipient tracing and notification in cases where the donor has CJD, nvCJD or risk factors for CJD.

This guidance document is released for immediate implementation. For the purpose of this guidance document, FDA interprets immediate implementation to mean as soon as feasible, but not later than April 17, 2000. FDA recognizes that the scientific technology for determining individuals at risk for CJD and nvCJD, and detecting the infectious agents in tissues and in products, is continuing to advance, and that there may be a need for future updating of the relevant guidance.

The guidance document represents the agency's current thinking on precautionary measures to reduce the possible risk and to assure that blood and blood products are not adulterated or misbranded, within the meaning of the Federal Food, Drug, and Cosmetic Act, and are safe, pure and potent within the meaning of the Public Health Service Act. 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. As with other guidance documents, FDA does not intend this document to be all-inclusive and cautions that not all information may be applicable to all situations. The document is intended to provide information and does not set forth requirements.

II. Comments

Interested persons, may at any time, submit to the Dockets Management Branch (address above) written comments regarding this guidance document. Two copies of any comments are to be submitted, except that

individuals may submit one copy. Comments should be identified with the docket number found in brackets in the heading of this document. A copy of the guidance document and received comments are available for public examination in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday.

III. Electronic Access

A copy of the guidance document may be obtained through FDA's Internet site at http://www.fda.gov/cber/guidelines.htm.

Dated: November 16, 1999.

Margaret M. Dotzel,

Acting Associate Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 99D–0529]

Guidance for Industry on Changes to an Approved NDA or ANDA; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a guidance for industry entitled ''Changes to an Approved NDA or ANDA.'' This guidance is intended to assist applicants in determining how they should report changes to an approved new drug application (NDA) or abbreviated new drug application (ANDA).

DATES: Written comments may be submitted at any time.

ADDRESSES: Copies of this guidance are available on the Internet at http://www.fda.gov/cder/guidance/index.htm. Submit written requests for single copies of this guidance for industry to the Drug Information Branch (HFD–210), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Send one self-addressed adhesive label to assist the office in processing your requests. Submit written comments on the guidance to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Nancy B. Sager, Center for Drug Evaluation and Research (HFD–357), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–5633; e-mail: pac314__70@cder.fda.gov, for questions about content of the guidance.

SUPPLEMENTARY INFORMATION: On November 21, 1997, the President signed the Food and Drug Administration Modernization Act (the Modernization Act) (Public Law 105–115). Section 116 of the Modernization Act amended the Food, Drug, and Cosmetic Act (the act) by adding section 506A (21 U.S.C. 356a), which provides requirements for making and reporting manufacturing changes to an approved application and for distributing a drug product made with such changes.

FDA is announcing the availability of a guidance for industry entitled ''Changes to an Approved NDA or ANDA Application.'' The purpose of this guidance is to provide recommendations to holders of NDA's and ANDA's who intend to make postapproval changes in accordance with section 506A of the act. This guidance covers recommended reporting categories for postapproval changes for drugs, other than specified biotechnology and specified synthetic biological products. Recommendations are provided for postapproval changes in: (1) Components and composition, (2) manufacturing sites, (3) manufacturing process, (4) specifications, (5) package, (6) labeling, (7) miscellaneous changes, and (8) multiple related changes. This guidance does not provide recommendations on the specific information that should be developed by the applicant to assess the effect of the change on the identity, strength (e.g., assay, content uniformity), quality (e.g., physical, chemical, and biological properties), purity (e.g., impurities and degradation products), or potency (e.g., biological activity, bioavailability, and bioequivalence) of a product as they may relate to the safety or effectiveness of the product.

In the **Federal Register** of June 28, 1999 (64 FR 34660), FDA announced the availability of a draft version of this guidance and gave interested persons an opportunity to submit comments through August 27, 1999. All comments received during the comment period have been carefully reviewed and incorporated in this revised guidance, where appropriate.

The agency received multiple comments on three specific issues. First, some comments objected to the agency's proposal to include as an example of an annual report change ''Any change made to comply with an official compendium that is consistent with FDA requirements and that provides the same or greater level of assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application.'' The agency has revised this example as recommended in the comments to state ''Any change made to comply with an official compendium.'' Second, the agency has removed from the guidance the recommendation ''list all changes included in the supplement or annual report in the cover letter.'' These issues, however, are still under consideration with regard to FDA's proposal to amend its regulations entitled *Supplements and other changes to an approved application* at § 314.70 (21 CFR 314.70), which published in the **Federal Register** of June 28, 1999 (64 FR 34608). If necessary, FDA will revise this guidance to make it consistent with the final rule for § 314.70.

Third, the agency received comments requesting that the phrase ''change that may affect sterility assurance,'' which is used throughout the guidance, be revised to, for example, ''change that may significantly affect sterility assurance'' or ''change that may adversely affect sterility assurance.'' FDA did not revise the guidance as suggested because the phrase as proposed in the guidance is consistent with the phrasing used in existing regulations (e.g., 21 CFR 601.12(b)(2)(vi)). If during the review of the comments on the proposed rule to amend § 314.70 FDA decides to revise this phrasing, this guidance will be revised to make it consistent with the final rule for § 314.70.

This guidance is being issued consistent with FDA's good guidance practices (62 FR 8961, February 27, 1997). It represents the agency's current thinking on how it will apply the requirements of section 506A of the act for NDA and ANDA products. 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.

FDA has established an e-mail address where an applicant can send questions about the content of the guidance, such as requesting clarification of information in the guidance or requesting guidance on the reporting category of particular change it wants to implement. The e-mail address is: pac314__70@cder.fda.gov.

This guidance document contains collections of information that require clearance by the Office of Management