to have an adverse effect on the product's safety, purity, potency, or effectiveness, shall be documented by the applicant in an annual report submitted each year within 60 days of the anniversary date of approval of the application. The annual report shall contain the following information for each change:

(i) A list of all products involved;

(ii) A brief description of and reason(s) for the change;

(iii) The manufacturing sites or areas involved;

(iv) The date each change was made; and

(v) A cross-reference to relevant validation protocol(s) and/or SOP's.

(2) The applicant shall submit the report to the FDA office responsible for reviewing the application. The report shall include all the information required under this section obtained for each change made during the annual reporting interval which ends on the anniversary date.

(e) *Labeling changes*—(1) *Label changes requiring supplement submission—distribution of a product with a label change must await FDA approval.* An applicant shall submit to CBER a supplement describing a proposed change in the package insert, package label, or container label, except those described in paragraphs (e)(2) and (e)(3) of this section, and include the information necessary to support the proposed change. The supplement shall clearly highlight the proposed change in the label. The applicant shall obtain approval from the Director, CBER, prior to distributing a product with the label change.

(2) *Label changes requiring supplement submission; product with a label change may be distributed before FDA approval.* (i) An applicant shall submit to CBER, at the time such change is made, a supplement for any change in the package insert, package label, or container label to accomplish any of the following:

(A) To add or strengthen a contraindication, warning, precaution, or adverse reaction;

(B) To add or strengthen a statement about abuse, dependence, psychological effect, overdosage;

(C) To add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the product; or

(D) To delete false, misleading, or unsupported indications for use or claims for effectiveness.

(ii) The applicant may distribute a product with a package insert, package label, or container label bearing such change at the time the supplement is submitted. The supplement shall clearly identify the change being made and include necessary supporting data. The supplement and its mailing cover should be plainly marked: ''Special Labeling Supplement—Changes Being Effected.''

(3) *Label changes requiring submission in an annual report.* (i) An applicant shall submit any final printed package insert, package label, or container label incorporating the following changes to CBER in an annual report submitted each year within 60 days of the anniversary date of approval of the application:

(A) Editorial or similar minor changes; or

(B) A change in the information on how the drug is supplied that does not involve a change in the dosage strength or dosage form.

(ii) The applicant may distribute a product with a package insert, package label, or container label bearing such change at the time the change is made.

(4) *Advertisements and promotional labeling.*

Advertisements and promotional labeling shall be submitted in accordance with the requirements set forth in § 314.81(b)(3)(i) of this chapter, except that Form FDA–2567 shall be used in lieu of Form FDA–2253.

(f) *Failure to comply.* In addition to other remedies available in law and regulations, in the event of repeated failure of the applicant to comply with this section, the Director, CBER, may require that the applicant submit a supplement for any proposed change to, and obtain approval of the supplement from, the Director, CBER, prior to distributing a product made using the change.

(g) *Administrative review.* Under § 10.75 of this chapter, an applicant may request internal FDA review of CBER employee decisions under this section.

Dated: January 16, 1996.

William B. Schultz,

Deputy Commissioner for Policy.

[FR Doc. 96–1580 Filed 1–25–96; 10:41 am]

BILLING CODE 4160–01–F

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21 CFR Parts 600 and 601

[Docket No. 95D–0415]

Draft Guidance; Changes To An Approved Application for Well-Characterized Therapeutic Recombinant DNA-Derived and Monoclonal Antibody Biotechnology Products; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule; notice of availability.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a draft guidance document entitled ''Draft Guidance; Changes to An Approved Application for Well-Characterized Therapeutic Recombinant DNA-Derived and Monoclonal Antibody Biotechnology Products.'' This draft guidance is intended to assist applicants in determining how they should report changes to an approved license application for well-characterized therapeutic recombinant DNA-derived and monoclonal antibody biotechnology products under the proposed revision to the biologics regulations issued elsewhere in this issue of the Federal Register. In a separate document also published in this issue of the Federal Register, FDA is announcing the availability of a guidance document to assist applicants in determining how they should report changes to an approved license application for biologic products other than well-characterized therapeutic recombinant DNA-derived and monoclonal antibody biotechnology products under the proposed rule. FDA does not intend for these draft guidance documents to be used at this time. The agency is providing these guidance documents for public comment only.

DATES: Written comments by April 29, 1996.

ADDRESSES: Submit written requests for single copies of the draft guidance entitled ''Draft Guidance; Changes to An Approved Application for Well-Characterized Recombinant DNA-Derived and Monoclonal Antibody Biotechnology Products'' to the Congressional and Consumer Affairs Branch (HFM–12), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448, 301–594–1800 or call FDA's automated information system at 800–835–4709. Send two self-addressed adhesive labels to assist that office in processing your requests. Submit written comments on the draft guidance to the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857. Two copies of any comments are to be submitted, except that individuals may submit one copy. Requests and comments should be identified with the docket number found in brackets in the heading of this document. A copy of the draft guidance and received comments are available for public examination in

the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

Persons with access to INTERNET may request that the draft guidance document be sent by return E-mail by sending a message to ''Character@A1.CBER.FDA.GOV''. The draft guidance document may also be obtained through INTERNET via File Transfer Protocol (FTP). Requestors should connect to the Center for Drug Evaluation and Research (CDER) using the FTP. The Center for Biologics Evaluation and Research (CBER) documents are maintained in a subdirectory called CBER on the server, ''CDVS2.CDER.FDA.GOV'' (150.148.24.202). The ''READ.ME'' file in that subdirectory describes the available documents that may be available as an ASCII text file (*.TXT), or a WordPerfect 5.1 document (*.w51), or both. A sample dialogue for obtaining the READ.ME file with a text-based FTP program would be:

FTP CDVS2.CDER.FDA.GOV
LOGIN: CHARACTER
<PASSWORD:CHARACTER><''Your E-mail address''>
BINARY
CD CBER
GET READ.ME
EXIT

The draft guidance document may also be obtained by calling the CBER FAX Information System (FAX-ON-DEMAND) at 301–594–1939 from a touch tone telephone.

FOR FURTHER INFORMATION CONTACT:

Tracey H. Forfa or Timothy W. Beth, Center for Biologics Evaluation and Research (HFM–630), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448, 301–594–3074; or

Yuan Yuan Chiu, Center for Drug Evaluation and Research (HFD–510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–3510.

Dated: January 16, 1996.

William B. Schultz,

Deputy Commissioner for Policy.

[FR Doc. 96–1581 Filed 1–25–96; 10:42 am]

BILLING CODE 4160–01–F

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21 CFR Parts 600 and 601

[Docket No. 95D–0052]

Changes To An Approved Application; Draft Guidance; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule; notice of availability.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a draft guidance document entitled ''Draft Guidance; Changes to An Approved Application.'' The draft guidance is intended to assist applicants in determining how they should report changes to an approved license application under the proposed revision to the biologics regulations issued elsewhere in this issue of the Federal Register. FDA does not intend for this draft guidance to be used at this time. The agency is providing this guidance at this time for public comment only.

DATES: Written comments by April 29, 1996.

ADDRESSES: Submit written requests for single copies of the draft guidance entitled ''Draft Guidance; Changes to An Approved Application'' to the Congressional and Consumer Affairs Branch (HFM–12), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448, or call FDA's automated information system at 800–835–4709. Send two self-addressed adhesive labels to assist that office in processing your requests. Submit written comments on the draft guidance to the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857. Two copies of any comments are to be submitted, except that individuals may submit one copy. Requests and comments should be identified with the docket number found in brackets in the heading of this document. A copy of the draft guidance and received comments are available for public examination in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

Persons with access to INTERNET may request that the draft guidance document be sent by return E-mail by sending a message to ''Changes@A1.CBER.FDA.GOV''. The draft guidance document may also be obtained through INTERNET via File Transfer Protocol (FTP). Requestors should connect to the Center for Drug Evaluation and Research (CDER) using the FTP. The Center for Biologics Evaluation and Research (CBER) documents are maintained in a subdirectory called CBER on the server, ''CDVS2.CDER.FDA.GOV'' (150.148.24.202). The ''READ.ME'' file in that subdirectory describes the available documents which may be available as an ASCII text file (*.TXT), or a WordPerfect 5.1 document (*.w51), or both. A sample dialogue for obtaining the READ.ME file with a text-based FTP program would be:

FTP CDVS2.CDER.FDA.GOV
LOGIN: CHANGES
<PASSWORD:CHANGES> <''Your E-mail address''>
BINARY
CD CBER
GET READ.ME
EXIT

The draft guidance document may also be obtained by calling the CBER FAX Information System (FAX-ON-DEMAND) at 301–594–1939 from a touch tone telephone.

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Tracey H. Forfa or Timothy W. Beth, Center for Biologics Evaluation and Research (HFM–630), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448, 301–594–3074; or

Yuan Yuan Chiu, Center for Drug Evaluation and Research (HFD–510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–3510.

SUPPLEMENTARY INFORMATION: In the Federal Register of April 6, 1995 (60 FR 17535), FDA published a guidance document intended to provide guidance to applicants on which changes in manufacturing procedures and establishments may be implemented with and/or without prior approval by the Director, CBER under § 601.12 (21 CFR 601.12). The Federal Register notice and guidance document were intended to reduce the burden of reporting changes on manufacturers and to facilitate the approval process.

In a continuing effort to achieve the reduction in reporting burden and to respond to comments received on the April 6, 1995, guidance document, FDA is proposing a revision to § 601.12 published elsewhere in this edition of the Federal Register. In addition, FDA is announcing the availability of a draft guidance document entitled, ''Changes to An Approved Application.'' The guidance document sets forth CBER's current interpretation of the proposed rule to amend § 601.12 as it applies to biologic products other than those considered to be well-characterized therapeutic recombinant DNA-derived and monoclonal antibody biotechnology products. The reporting mechanisms proposed in the rule are based on the potential for the change to affect a product's safety, purity, potency, and effectiveness. In a separate document also published in this issue of the Federal Register, FDA is announcing