Delay of Effective Date

The effective date of the final rule, Airspace Docket 93–AWA–5, as published in the **Federal Register** on November 30, 1998 (63 FR 65972), is hereby delayed until further notice.

Authority: 49 U.S.C. 106(g), 40103, 40113, 40120; E.O. 10854, 24 FR 9565, 3 CFR, 1959–1963 Comp., p. 389.

Issued in Washington, DC, on December 7, 1998.

John S. Walker,

Program Director for Air Traffic Airspace Management.

[FR Doc. 98–33094 Filed 12–11–98; 8:45 am]

BILLING CODE 4910–13–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 312

[Docket No. 98N–0979]

Investigational New Drug Applications; Clinical Holds

AGENCY: Food and Drug Administration, HHS.

ACTION: Direct final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its regulations governing investigational new drug applications (IND's) for human drug and biological products. This action amends the IND clinical hold requirements to state that the agency will respond in writing to a sponsor's request that a clinical hold be removed from an investigation within 30-calendar days of the agency's receipt of the request and the sponsor's complete response to the issue(s) that led to the clinical hold. FDA is taking this action in accordance with provisions of the Food and Drug Administration Modernization Act of 1997 (the Modernization Act). Elsewhere in this issue of the **Federal Register**, FDA is publishing a companion proposed rule under FDA's usual procedure for notice-and-comment rulemaking to provide a procedural framework to finalize the rule in the event the agency receives significant adverse comments and withdraws this direct final rule.

DATES: This regulation is effective April 28, 1999. Submit written comments on or before March 1, 1999. If no timely significant adverse comments are received, the agency will publish a document in the **Federal Register** before March 29, 1999, confirming the effective date of the direct final rule. If timely significant adverse comments are received, the agency will publish a document of significant adverse comment in the **Federal Register** withdrawing this direct final rule before March 29, 1999.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT:

Murray M. Lumpkin, Center for Drug Evaluation and Research (HFD–2), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–5400, or

Rebecca A. Devine, Center for Biologics Evaluation and Research (HFM–10), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852, 301–827–0373.

SUPPLEMENTARY INFORMATION:

I. Discussion

A. Introduction

On November 21, 1997, President Clinton signed into law the Modernization Act (Pub. L. 105–115). Section 117 of the Modernization Act amends the Federal Food, Drug, and Cosmetic Act (the act) by codifying in section 505(i) (21 U.S.C. 355(i)) several of the procedures and requirements governing the use of investigational new drugs that are already set forth in FDA's regulations (parts 50 and 312 (21 CFR parts 50 and 312)).

Section 505(i)(2) of the act, as amended by the Modernization Act, provides that if a sponsor of an IND that has been placed on clinical hold requests in writing that the clinical hold be removed and submits a complete response to the issue(s) identified in the clinical hold order, FDA is required to respond in writing to the sponsor within 30-calendar days of receipt of the complete response. This direct final rule amends § 312.42(e) to reflect this new statutory requirement and to clarify when a sponsor may resume an investigation after FDA issues a clinical hold order.

In the **Federal Register** of May 14, 1998 (63 FR 26809), FDA announced the availability of a guidance document entitled ''Submitting and Reviewing Complete Responses to Clinical Holds.'' This guidance to industry describes how applicants should submit responses to clinical holds so that they may be identified as complete responses.

B. Background

The procedures and requirements governing the use of investigational new drugs, including the submission and review of IND's, are set forth in part 312. An investigational new drug is a new drug or biological drug that is used in a clinical investigation. A clinical investigation is an experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. An investigational new drug that meets the requirements of part 312 is exempt from the premarket approval requirements that are otherwise applicable, and may be shipped lawfully for the purpose of conducting clinical investigations of the drug.

Part 312 applies to all clinical investigations of products that are subject to section 505 of the act, or to the licensing provisions of section 351 of the Public Health Service Act (42 U.S.C. 262), with one principal exemption—certain clinical investigations of drugs that have received premarket approval and are lawfully marketed.

The person who takes responsibility for and initiates a clinical investigation of an investigational new drug is the IND sponsor. The sponsor may be an individual, a pharmaceutical company, a government agency, an academic institution, or other entity. The individual who actually conducts a clinical investigation and administers the investigational drug to patients is the investigator (the investigator may also be the sponsor). Responsibilities of a sponsor include: (1) Notifying FDA of any serious and unexpected adverse experience associated with the use of the drug; (2) selecting qualified investigators and overseeing the conduct of those investigators; (3) ensuring that the investigations are performed in accordance with the investigational plan and protocols contained in the IND; (4) providing investigators with an investigator's brochure; and (5) submitting an annual report to FDA.

A sponsor may not begin clinical testing with an investigational new drug until an IND is submitted to FDA and is in effect for that drug. The IND content and format requirements are set forth in § 312.23. An IND automatically becomes effective 30-calendar days after FDA receives the initial IND submission (or earlier upon FDA's notification), unless FDA informs the sponsor that the investigation may not proceed (i.e., a clinical hold is issued).

A clinical hold is an order that FDA issues to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. Section 505(i) of the act, as amended by the Modernization Act, verifies FDA's authority to issue a clinical hold and

endorses FDA regulations that describe the grounds upon which a clinical hold may be issued. Under such regulations, codified in § 312.42, the basis for a clinical hold depends on the phase of the clinical study. FDA may place a proposed or ongoing Phase 1 investigation on clinical hold if it finds any of the following: (1) Unreasonable and significant risk of illness or injury; (2) unqualified clinical investigators; (3) a misleading, erroneous, or materially incomplete investigator brochure; or (4) insufficient information in the IND to assess the risks to subjects. A Phase 2 or Phase 3 study may be suspended for any of these reasons or, in addition, because it is deficient in design to meet its stated objectives. The clinical hold regulations specify additional grounds for placing a hold on a treatment IND or treatment protocol or any study not designed to be adequate and well-controlled (§ 312.42(b)(3) and (b)(4)). An investigation that has been placed on clinical hold may resume only after the deficiency that prompted the clinical hold is corrected by the sponsor and the hold has been released by FDA.

C. Description of the Direct Final Rule

Current § 312.42(e) describes when a clinical investigation may resume after a clinical hold has been imposed by FDA. An investigation may resume after the Division Director with responsibility for review of the IND notifies the sponsor that the investigation may proceed. This notification is usually made after the sponsor corrects the deficiency or deficiencies that resulted in the clinical hold. Resumption of an investigation may be authorized by telephone or other means of rapid communication. Under the current regulation, no timeframe is given within which FDA will notify the sponsor that an investigation may resume after the sponsor has submitted answers to the deficiencies that resulted in the clinical hold and has requested that FDA remove the clinical hold.

As explained previously, FDA is now required under section 505(i)(2) of the act to respond to a written request from a sponsor that a clinical hold be removed within 30-calendar days of receipt of the request and the sponsor's complete response to the issue(s) that led to the clinical hold. Therefore, FDA is amending § 312.42(e) to reflect this requirement. In requesting that the clinical hold be removed, the sponsor of the IND must address all of the clinical hold issues that the agency noted in the clinical hold order. FDA may notify the sponsor of its decision on the request to release the clinical hold by telephone or other means of rapid communication, but a written response will be issued within 30-calendar days of receipt of the sponsor's request and complete response to the issue(s) that led to the clinical hold. If FDA determines that the clinical hold will be maintained, the written response will state the reasons for such decision.

In addition, under current § 312.42(e), the terms of certain clinical holds may permit an investigation to resume without FDA's prior notification once the correction or modification that caused the clinical hold is made. FDA is deleting the first sentence of current § 312.42(e) because it does not accurately reflect the agency's practice in imposing a clinical hold. The types of concerns that FDA might raise with regard to a clinical investigation that could be remedied and implemented without prior agency notification do not require the imposition of a clinical hold. Such concerns are generally resolved through discussions between the sponsor and FDA. FDA generally imposes a clinical hold on an investigation if the deficiencies are such that the study's resumption would require prior approval by the agency. This revision will help eliminate any confusion regarding whether a clinical hold has been placed and the process of removing a clinical hold from an investigation and any inconsistent treatment of IND's by different units within FDA.

II. Direct Final Rulemaking

FDA has determined that this amendment to the agency's regulations governing IND's for human drug and biological products is suitable for a direct final rule. The actions taken should be noncontroversial and the agency does not anticipate receiving any significant adverse comments. This direct final rule amends § 312.42(e) to reflect section 117 of the Modernization Act and current agency practice in imposing a clinical hold.

If FDA does not receive significant adverse comment on or before March 1, 1999, the agency will publish a document in the **Federal Register** before March 29, 1999, confirming the effective date of the direct final rule. A significant adverse comment is one that explains why the rule would be inappropriate, including challenges to the rule's underlying premise or approach, or would be ineffective or unacceptable without a change. A comment recommending a rule change in addition to this rule will not be considered a significant adverse comment, unless the comment states why this rule would be ineffective without the additional change. If timely significant adverse comments are received, the agency will publish a notice of significant adverse comment in the **Federal Register** withdrawing this direct final rule before March 29, 1999.

Elsewhere in this issue of the **Federal Register**, FDA is publishing a companion proposed rule, which is identical to the direct final rule, that provides a procedural framework within which the rule may be finalized in the event the direct final rule is withdrawn because of significant adverse comment. The comment period for the direct final rule runs concurrently with that of the companion proposed rule. Any comments received under the companion proposed rule will be treated as comments regarding the direct final rule. Likewise, significant adverse comments submitted to the direct final rule will be considered as comments to the companion proposed rule and the agency will consider such comments in developing a final rule. FDA will not provide additional opportunity for comment on the companion proposed rule.

If a significant adverse comment applies to part of this rule and that part may be severed from the remainder of the rule, FDA may adopt as final those parts of the rule that are not the subject of a significant adverse comment. A full description of FDA's policy on direct final rule procedures may be found in a guidance document published in the **Federal Register** of November 21, 1997 (62 FR 62466).

III. Environmental Impact

The agency has determined under 21 CFR 25.30(h) that this action is of a class of actions that do not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IV. Analysis of Impact

FDA has examined the impacts of this direct final rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Executive Order 12866 classifies a rule as significant if it meets any one of a number of specified conditions, including having an annual effect on the

economy of $100 million or adversely affecting in a material way a sector of the economy, competition, or jobs, or if it raises novel legal or policy issues. The agency believes that this rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the rule is not a significant regulatory action as defined by the Executive Order and so is not subject to review under the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options to minimize any significant impact on small entities. The agency has considered the effect that this rule will have on small entities, including small businesses, and certifies that the rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

The Unfunded Mandates Reform Act requires an agency to prepare a budgetary impact statement before issuing any rule likely to result in a Federal mandate that may result in expenditures by State, local, and tribal governments or the private sector of $100 million (adjusted annually for inflation) in any 1 year. This rule will not result in an expenditure of $100 million or more on any governmental entity or the private sector, so no budgetary impact statement is required.

V. Paperwork Reduction Act of 1995

This direct final rule contains no collections of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

VI. Request for Comments

Interested persons may, on or before March 1, 1999, submit to the Dockets Management Branch (address above) written comments regarding this rule. 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. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR Part 312

Drugs, Exports, Imports, Investigations, Labeling, Medical research, Reporting and recordkeeping requirements, Safety.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 312 is amended to read as follows:

PART 312—INVESTIGATIONAL NEW DRUG APPLICATION

1. The authority citation for 21 CFR part 312 is revised to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 371; 42 U.S.C. 262.

2. Section 312.42 is amended by revising paragraph (e) to read as follows:

§ 312.42 Clinical holds and requests for modification.

* * * * *

(e) *Resumption of clinical investigations.* An investigation may only resume after FDA (usually the Division Director, or the Director's designee, with responsibility for review of the IND) has notified the sponsor that the investigation may proceed. Resumption of the affected investigation(s) will be authorized when the sponsor corrects the deficiency(ies) previously cited or otherwise satisfies the agency that the investigation(s) can proceed. FDA may notify a sponsor of its determination regarding the clinical hold by telephone or other means of rapid communication. If a sponsor of an IND that has been placed on clinical hold requests in writing that the clinical hold be removed and submits a complete response to the issue(s) identified in the clinical hold order, FDA shall respond in writing to the sponsor within 30-calendar days of receipt of the request and the complete response. FDA's response will either remove or maintain the clinical hold, and will state the reasons for such determination. Notwithstanding the 30-calendar day response time, a sponsor may not proceed with a clinical trial on which a clinical hold has been imposed until the sponsor has been notified by FDA that the hold has been lifted.

* * * * *

Dated: December 4, 1998.

William B. Schultz,

Deputy Commissioner for Policy.

[FR Doc. 98–33029 Filed 12–11–98; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF THE TREASURY

Internal Revenue Service

26 CFR Parts 1 and 602

[TD 8795]

RIN 1545–AT78

Notice of Significant Reduction in the Rate of Future Benefit Accrual

AGENCY: Internal Revenue Service (IRS), Treasury.

ACTION: Final regulations.

SUMMARY: This document contains final regulations that provide guidance on the requirements of section 204(h) of the Employee Retirement Income Security Act of 1974, as amended (ERISA), relating to defined benefit plans and to individual account plans that are subject to the funding standards of section 302 of ERISA. It requires the plan administrator to give notice of plan amendments, which provide for a significant reduction in the rate of future benefit accural, to participants in the plan and certain other parties.

DATES: Effective Date: December 14, 1998.

Applicability Dates: For dates of applicability of these regulations, see Effective Dates under Supplementary Information.

FOR FURTHER INFORMATION CONTACT: Diane S. Bloom at (202)622–6214 or Christine L. Keller at (202)622–6090 (not toll-free numbers).

SUPPLEMENTARY INFORMATION:

Paperwork Reduction Act

The collection of information contained in these final regulations has been reviewed and approved by the Office of Management and Budget in accordance with the Paperwork Reduction Act of 1995 (44 U.S.C. 3705(d)) under the control number 1545–1477. The collection of information in these final regulations is in § 1.411(d)–6. Responses to this collection of information are required in order to obtain a benefit. Specifically, this information is required for a taxpayer who wants to amend a qualified plan to significantly reduce the rate of future benefit accrual. This information will be used to notify participants, alternate payees and employee organizations of the amendment.

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a valid control number.

The estimated average burden per recordkeeper varies from 1 hour to 40