4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 56

[Docket No. FDA-2015-N-5052]

Administrative Actions for Noncompliance; Lesser Administrative Actions

AGENCY: Food and Drug Administration, HHS.

ACTION: Direct final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the regulation describing lesser administrative actions that may be imposed on an Institutional Review Board (IRB) that has failed to comply with FDA's IRB regulations. We are clarifying that FDA may require the IRB to withhold approval of new FDA-regulated studies, stop the enrollment of new subjects in ongoing studies, and terminate ongoing studies, or any combination of these actions until the noncompliance with FDA's IRB regulations is corrected. We are taking this action to ensure clarity and improve the accuracy of the regulations.

DATES: This rule is effective [INSERT DATE 135 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER]. Submit electronic or written comments on this direct final rule or its companion proposed rule by [INSERT DATE 75 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

ADDRESSES: You may submit comments as follows:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: http://www.regulations.gov. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to http://www.regulations.gov will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on http://www.regulations.gov.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Division of Dockets Management, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2015-N-5052 for "Subpart E--Administrative Actions for Noncompliance; Lesser Administrative Actions." Received comments will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at http://www.regulations.gov or at the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on http://www.regulations.gov. Submit both copies to the Division of Dockets Management. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: http://www.fda.gov/regulatoryinformation/dockets/default.htm.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to http://www.regulations.gov and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Sheila Brown, Office of Good Clinical Practice, Office of Special Medical Programs, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 32, rm. 5129, Silver Spring, MD 20993-0002, 301-796-6563.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is amending § 56.120(b) (21 CFR 56.120(b)), which describes lesser administrative actions that the Agency may impose on an IRB until the IRB takes appropriate action to correct the IRB's noncompliance. We are publishing this direct final rule because it is intended to clarify an existing regulation, and we do not anticipate any significant adverse comment regarding this amendment to § 56.120(b). Specifically, this direct final rule would amend § 56.120(b) by clarifying that FDA has authority to require the IRB to withhold approval of new FDA-regulated studies conducted at the institution or reviewed by the IRB, direct that no new subjects be added to ongoing studies, and terminate ongoing studies provided that doing so would not endanger study subjects.

This amendment also renumbers current paragraphs (b)(4) and (c) as paragraphs (c) and (d), respectively, and inserts “FDA may” into newly designated paragraph (c) so that it is a complete sentence.

FDA first proposed requirements for the composition and operations of institutional review committees in the "Proposed Investigational Device Exemptions," published in the Federal Register of August 20, 1976 (41 FR 35282; "Proposed IDE Rule"). In that document, FDA proposed disqualification procedures for institutional review committees and requested comments on the proposed procedures and other possible administrative actions that FDA might take against a committee that is not in compliance with the regulations (41 FR 35282 at 35293). FDA also stated its intention to publish uniform, Agency-wide regulations governing clinical investigations at a later date, including requirements governing institutional review committees (41 FR 35282 at 35283).

Subsequently, FDA published "Standards for Institutional Review Boards for Clinical Investigations" on August 8, 1978 (43 FR 35186; "Proposed IRB Standards"). Comments on implementing institutional review requirements received in response to the Proposed IDE Rule were reviewed and utilized in preparing the Proposed IRB Standards (43 FR 35186 at 35187). In the Proposed IRB Standards, FDA proposed that disqualification would be used only if the Commissioner of Food and Drugs finds that: (1) The IRB failed to comply with one or more of the standards for IRBs in part 56 or other supplemental requirements in the investigational new drug or investigational device exemptions (IDE) regulations; (2) the noncompliance adversely affects the validity of the data or the rights or safety of the human subjects; and (3) other lesser regulatory actions (e.g., warnings or rejection of data from individual clinical investigations) have not been or probably will not be adequate in achieving compliance (43 FR 35186 at 35195).

FDA received numerous comments to the Proposed IRB Standards, and addressed those comments in the Federal Register of January 27, 1981 (46 FR 8958), "Protection of Human

Subjects: Standards for Institutional Review Boards for Clinical Investigations, Final Rule." Specifically, several comments suggested that any lesser regulatory actions should be listed (46 FR 8958 at 8973). FDA accepted these comments and revised § 56.120(b) to set forth the lesser administrative actions that the Agency may take if FDA finds deficiencies in the operation of an IRB and to describe the circumstances in which these lesser administrative actions may be used by the Agency. FDA's longstanding interpretation of § 56.120(b) is that FDA may impose these restrictions on a noncompliant IRB until the IRB takes appropriate corrective action. The text of the regulation, however, suggests that it is the Agency that would withhold approval of studies that have been reviewed by a noncompliant IRB, rather than authorizing FDA to direct the IRB to stop approving new studies until the IRB comes back into compliance.

This direct final rule amends § 56.120(b) to read, in addition, until the IRB or the parent institution takes appropriate corrective action, the Agency may require the IRB to withhold approval of new studies, direct that no new subjects be added to ongoing studies, or terminate ongoing studies. This will ensure that those activities are suspended until the IRB takes appropriate corrective action to address its noncompliance. We believe revising § 56.120(b) as described in this document will improve the clarity and accuracy of the regulations. We are also renumbering § 56.120(b)(4) as § 56.120(c), and § 56.120(c) as § 56.120(d). We are inserting "FDA may" into newly designated § 56.120(c) so that it is a complete sentence.

FDA may notify relevant State and Federal regulatory Agencies when warranted to assure that organizations with a need to know about the IRB's apparent noncompliance are appropriately informed. The revision would eliminate confusion by stating clearly that FDA is authorized to notify others about the IRB's noncompliance. We believe these changes will ensure clarity and improve the accuracy of the regulations.

II. Procedures for Issuing a Direct Final Rule

In the Federal Register of November 21, 1997 (62 FR 62466), FDA announced the availability of the guidance document entitled "Guidance for FDA and Industry: Direct Final Rule Procedures"[1] that described when and how we will employ direct final rulemaking. We believe that this rule is appropriate for direct final rulemaking because it is intended to clarify an existing regulation. We anticipate no significant adverse comment.

Consistent with FDA's direct final rulemaking procedures, we are publishing a companion proposed rule elsewhere in this issue of the Federal Register. That proposed rule is identical in substance to this direct final rule. The companion proposed rule will serve the purpose of issuing a proposed rule under usual notice-and-comment procedures in the event we withdraw this direct final rule because we receive significant adverse comment. The comment period for this direct final rule runs concurrently with the comment period of the companion proposed rule. We will consider any comments that we receive in response to the companion proposed rule to be comments also regarding this direct final rule and vice versa.

If FDA receives any significant adverse comment, we will withdraw this direct final rule before its effective date by publishing a notice in the Federal Register within 30 days after the comment period ends. 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. In determining whether an adverse comment is significant and warrants withdrawing a direct final rule, we consider whether the comment raises an issue serious enough to warrant a substantive response in a notice-and-comment process in accordance with section 553 of the Administrative Procedure Act (APA) (5 U.S.C. 553).

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[1] http://www.fda.gov/regulatoryinformation/guidances/ucm125166.htm.

Comments that are frivolous, insubstantial, or outside the scope of the rule would not be considered adverse. A comment recommending a rule change in addition to the rule would not be considered a significant adverse comment, unless the comment states why the rule would be ineffective without the additional change. In addition, if a significant adverse comment applies to part of a rule and that part can be severed from the remainder of the rule, we may adopt as final those parts of the rule that are not the subject of a significant adverse comment.

If we withdraw this direct final rule, FDA will consider all comments that we received regarding the companion proposed rule as we develop a final rule through the usual notice-and-comment procedures of the APA. If we receive no significant adverse comment during the specified comment period regarding this direct final rule, we intend to publish a confirmation notice in the Federal Register within 30 days after the comment period ends.

III. Legal Authority

This rule, if finalized, would amend § 56.120(b). FDA's authority to modify § 56.120(b) arises from the same authority under which FDA initially issued this regulation, the IRB regulations, and general administrative provisions of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 343, 346, 346a, 348, 350a, 350b, 351, 352, 353, 355, 360, 360c-360f, 360h, 360i, 360j, 360hh-360ss, 371, 379e, 381; 42 U.S.C. 216, 241, 262).

IV. Analysis of Environmental Impact

We have determined under 21 CFR 25.30(h) and 25.34(a) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

V. Economic Analysis of Impact

We have examined the impacts of the final rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). Executive Orders 12866 and 13563 direct us 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). We believe that this final rule is not a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because this rule does not add any additional regulatory burdens, we certify that this final rule will not have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires us to prepare a written statement, which includes an assessment of anticipated costs and benefits, before issuing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is $144 million, using the most current (2014) Implicit Price Deflator for the Gross Domestic Product. This final rule would not result in an expenditure in any year that meets or exceeds this amount.

The purpose of this final rule is to affirm FDA's longstanding interpretation of § 56.120(b), that FDA may impose these administrative actions on a noncompliant IRB until the IRB takes appropriate corrective action. The amendment will improve the clarity and accuracy of the regulations. Because this final rule is a clarification and would impose no additional

regulatory burdens, this regulation is not anticipated to result in any compliance costs, and the economic impact is expected to be minimal.

VI. Paperwork Reduction Act of 1995

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

VII. Federalism

We have analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the Agency has concluded that the rule does not contain policies that have federalism implications as defined in the Executive Order and, consequently, a federalism summary impact statement is not required.

List of Subjects in 21 CFR Part 56

Human research subjects, Reporting and recordkeeping requirements, Safety.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 56 is amended as follows:

PART 56--INSTITUTIONAL REVIEW BOARDS

1. The authority citation for 21 CFR part 56 is revised to read as follows:

Authority: 21 U.S.C. 321, 343, 346, 346a, 348, 350a, 350b, 351, 352, 353, 355, 360, 360c-360f, 360h, 360i, 360j, 360hh-360ss, 371, 379e, 381; 42 U.S.C. 216, 241, 262.

2. In § 56.120, redesignate paragraphs (b)(4) and (c) as paragraphs (c) and (d), respectively, and revise paragraph (b) and newly designated paragraph (c) to read as follows:

§ 56.120 Lesser administrative actions.

* * * * *

(b) On the basis of the IRB's or the institution's response, FDA may schedule a reinspection to confirm the adequacy of corrective actions. In addition, until the IRB or the parent institution takes appropriate corrective action, the Agency may require the IRB to:

(1) Withhold approval of new studies subject to the requirements of this part that are conducted at the institution or reviewed by the IRB;

(2) Direct that no new subjects be added to ongoing studies subject to this part; or

(3) Terminate ongoing studies subject to this part when doing so would not endanger the subjects.

(c) When the apparent noncompliance creates a significant threat to the rights and welfare of human subjects, FDA may notify relevant State and Federal regulatory agencies and other parties with a direct interest in the Agency's action of the deficiencies in the operation of the IRB.

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Dated: March 29, 2016.

Leslie Kux,

Associate Commissioner for Policy.

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