Subtitle VII, Aviation Programs, describes in more detail the scope of the agency's authority.

This rulemaking is promulgated under the authority described in Subtitle VII, Part A. Subpart I, Section 40103. Under that section, the FAA is charged with prescribing regulations to assign the use of airspace necessary to ensure the safety of aircraft and the efficient use of airspace. This regulation is within the scope of that authority as it amends controlled airspace at Smithfield, NC.

Lists of Subjects in 14 CFR Part 71

Airspace, Incorporation by reference, Navigation (Air).

Adoption of the Amendment

■ In consideration of the foregoing, the Federal Aviation Administration amends 14 CFR Part 71 as follows:

PART 71—DESIGNATION OF CLASS A, B, C, D, AND E AIRSPACE AREAS; AIR TRAFFIC SERVICE ROUTES; AND REPORTING POINTS

■ 1. The authority citation for Part 71 continues to read as follows:

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

§ 71.1 [Amended]

■ 2. The incorporation by reference in 14 CFR 71.1 of Federal Aviation Administration Order 7400.9U, Airspace Designations and Reporting Points, dated August 18, 2010, and effective September 15, 2010, is amended as follows:

Paragraph 6005 Class E Airspace Extending Upward From 700 feet or More Above the Surface of the Earth

* * * * *

ASO NC E5 Smithfield, NC [Amended]

Johnston County Airport, NC
(Lat. 35°32′27″ N., long 78°23′25″ W.)
Johnston Memorial Hospital
Point In Space Coordinates
(Lat. 35°31′23″ N., long 78°20′35″ W.)

That airspace extending upward from 700 feet above the surface within a 6.5-mile radius of the Johnston County Airport and within 2 miles each side of the 023° bearing from the airport extending from the 6.5-mile radius to 10.2 miles northeast of the Johnston County Airport and within a 6-mile radius of the point in space (lat.35°31′23″ N., long. 78°20′35″ W.) serving Johnston Memorial Hospital.

Issued in College Park, Georgia, on September 17, 2010.

Myron A. Jenkins,

Acting Manager, Operations Support Group, Eastern Service Center, Air Traffic Organization.

[FR Doc. 2010–24113 Filed 9–28–10; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 312 and 320

[Docket No. FDA–2000–N–0108] (formerly Docket No. 00N–1484)

RIN 0910–AG13

Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its regulations governing safety reporting requirements for human drug and biological products subject to an investigational new drug application (IND). The final rule codifies the agency's expectations for timely review, evaluation, and submission of relevant and useful safety information and implements internationally harmonized definitions and reporting standards. The revisions will improve the utility of IND safety reports, reduce the number of reports that do not contribute in a meaningful way to the developing safety profile of the drug, expedite FDA's review of critical safety information, better protect human subjects enrolled in clinical trials, subject bioavailability and bioequivalence studies to safety reporting requirements, promote a consistent approach to safety reporting internationally, and enable the agency to better protect and promote public health.

DATES: This rule is effective March 28, 2011.

FOR FURTHER INFORMATION CONTACT:

For information on IND safety reporting for human drug products: Janet Norden, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 6324, Silver Spring, MD 20993–0002, 301–796–2500.

For information on IND safety reporting for human biological products: Laura Rich, Center for Biologics Evaluation and Research, Food and Drug Administration,1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448, 301–827–6210.

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I. Background

In the **Federal Register** of March 14, 2003 (68 FR 12406), FDA issued a proposed rule to revise its regulations governing pre- and postmarketing safety

reporting for human drug and biological products[1], which appear in parts 310, 312, 314, 320, 600, 601, and 606 (21 CFR parts 310, 312, 314, 320, 600, 601, and 606). The proposed revisions represented a major effort to clarify and integrate several safety reporting rules and guidance documents that had been issued by international organizations and by FDA dating back to the 1990s. The background for and description of these regulations and guidance documents are described in the preamble of the proposed rule (68 FR 12406 at 12407 to 12410, Figure 1). The proposal called for the submission of comments by July 14, 2003. At the request of industry, and to provide all interested persons additional time to comment, the comment period was extended until October 14, 2003 (68 FR 36527, June 18, 2003).

FDA received numerous comments in response to the proposed rule, many of which stated that the proposal would not meet its stated goals and requested that the agency reevaluate specific aspects of the proposal. FDA agreed with some of these comments and has reevaluated and revised aspects of the proposal. To make the rulemaking process more manageable, FDA has decided to issue revisions to the premarketing and postmarketing safety reporting regulations in two separate rulemakings. By separating these rules, the agency has been able to reevaluate and refine each requirement in the premarketing and postmarketing settings to better ensure that the rules will achieve their goals.

This rule finalizes revisions to the IND safety reporting regulations found in part 312 and the safety reporting requirements for bioavailability and bioequivalence studies found in part 320. The agency is working on revisions to the postmarketing safety reporting regulations found in parts 310, 314, 600, 601, and 606 separately, and will address these sections in a future rule. Therefore, revisions to and comments about postmarketing safety reporting requirements found in parts 310, 314, 600, 601, and 606 are not addressed in this rulemaking. This document discusses information relevant to and comments about the proposed revisions found in parts 312 and 320.

A. Rationale for Rulemaking

In the proposed rule (68 FR 12406 at 12412 to 12415), FDA described its goals for the proposed rulemaking. Many of the stated goals were primarily applicable to postmarketing safety reporting, but revising and clarifying the IND safety reporting requirements was also a critical component of FDA's stated efforts to: (1) Improve the overall quality of safety reporting, thereby strengthening the agency's ability to review critical safety information, (2) monitor the safety of human drug and biological products, and (3) harmonize safety reporting internationally. Each of these is discussed in turn in this document.

First, the revisions to the IND safety reporting requirements will improve the overall quality of safety reporting and the agency's ability to review critical safety information by ensuring that the information that FDA receives in an IND safety report is relevant and useful. Under former regulations, there may have been over-reporting of serious adverse events for which there was little reason to believe that the drug had caused the event, complicating or delaying FDA's ability to detect a safety signal. In this final rule, FDA clarifies definitions, provides examples of the types of evidence that suggest a causal relationship for purposes of reporting a suspected adverse reaction to the IND and participating investigators, and revises the requirements for expedited reporting of serious and unexpected suspected adverse reactions to the IND. The final rule also allows sponsors to arrange alternative formats and/or frequencies for reporting and provides that study endpoints must not be submitted as IND safety reports except in unusual cases. These revisions not only have an impact on which reports are sent to FDA and participating investigators, but also affect the reports that are sent by investigators to Institutional Review Boards (IRBs). These revisions and clarifications will minimize reports that do not contribute to FDA's understanding of the developing safety profile of the drug and decrease the number of uninterpretable reports (so-called "noise") in the system. In addition, the revisions and clarifications will help to make clear under what circumstances the study blind should be broken and when unblinding is unnecessary. Ultimately, these revisions and clarifications should contribute toward more useful adverse reaction information and more effective monitoring of clinical trials.

Second, by requiring expedited reports of certain safety information that was not reported expeditiously under former IND safety reporting requirements or bioavailability or bioequivalence requirements, the final rule will help FDA monitor the safety of human drug and biological products and better protect human subjects enrolled in clinical trials. Under the final rule, FDA will receive expedited reports of:

- Findings from clinical studies, epidemiological studies or pooled analyses of multiple studies that suggest a significant risk in humans exposed to the drug,
- Serious suspected adverse reactions that occur at an increased rate than listed in the protocol or investigator brochure, and
- Serious adverse events from bioavailability and bioequivalence studies.

By receiving these reports expeditiously, FDA will be better able to monitor and evaluate the drug's safety.

Finally, FDA had proposed certain revisions to its IND safety reporting requirements to harmonize the regulations with recommendations by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and by the World Health Organization's Council for International Organizations of Medical Sciences (CIOMS), and which have been adopted by the European Union (EU) (Ref. 1). In the preamble to the proposed rule (68 FR 12406 at 12415, table 4), FDA detailed the specific proposed revisions to the definitions and reporting standards based on international recommendations in the ICH guidance "E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting" (60 FR 11284, March 1, 1995) (ICH E2A guidance). FDA received numerous comments, described in more detail in section III of this document, stating that certain of FDA's proposed revisions were inconsistent with how the provisions are interpreted and implemented in other member ICH nations. After reviewing the comments and after discussions with our ICH partners, FDA has revised the definitions and reporting standards to be as consistent as possible with international definitions and standards, recognizing that there may be inconsistencies within ICH documents and among the other member ICH nations' interpretations of these definitions and standards.

B. The Proposed Rule

The following describes the proposed revisions to the requirements in parts 312 and 320. FDA proposed the following revisions to § 312.32 on IND safety reports:

- Replace the defined phrase "associated with the use of the drug"

[1] For the purposes of this document, unless otherwise specified, all references to "drugs" or "drug products" include human drug products and biological products that are also drugs.

with the term "suspected adverse drug reaction (SADR),"

- Require submission of expedited reports of "information sufficient to consider product administration changes,"
- Make it clear that safety reports of overall findings or data in the aggregate must be submitted in a narrative format,
- Permit the determination that an SADR is life-threatening to be based on the opinion of either the investigator or sponsor (as opposed to only the investigator),
- Require that the sponsor notify FDA and all participating investigators of each SADR that is both serious and unexpected, based on the opinion of either the investigator or sponsor (as opposed to only the sponsor),
- Require a ""minimum data set" for each report of an SADR submitted to FDA, and
- Clarify the sources of information that sponsors must review for safety surveillance and reporting purposes.

FDA proposed the following revision to § 312.64(b):

- Make it clear that the investigator must report to the sponsor any serious SADR immediately and any other SADR promptly, unless otherwise specified in the protocol or investigator's brochure.

FDA proposed the following revision to § 320.31(d):

- Make bioavailability and bioequivalence studies subject to IND safety reporting requirements.

II. Overview of the Final Rule

This final rule amends parts 312 and 320 of FDA regulations by revising the requirements for IND safety reporting and for bioavailability and bioequivalence studies. This final rule reflects revisions the agency made in response to comments on the March 2003 proposal (addressed in detail in section III of this document) and other revisions, including editorial changes to clarify provisions and support the agency's plain language initiative (addressed in this section).

A. Definitions

The definitions section for the IND safety reporting regulations (§ 312.32(a)) now includes the following five terms:

- Adverse event,
- Life-threatening adverse event or life-threatening suspected adverse reaction,
- Serious adverse event or serious suspected adverse reaction,
- Suspected adverse reaction, and
- Unexpected adverse event or unexpected suspected adverse reaction.

FDA has revised and clarified terms and definitions that were in the proposed rule. First, as discussed in detail in section III of this document, the two terms "adverse event" and "suspected adverse reaction" replace the proposed definition of "suspected adverse drug reaction (SADR)." The definitions "adverse event" and "suspected adverse reaction" also replace the phrase "associated with the use of the drug" defined in former § 312.32(a). The definitions of the terms "adverse event" and "suspected adverse reaction" make clear a distinction in the degree of evidence of a causal relationship between the drug and the adverse event within these terms.

Second, the final rule requires that the determination for reporting purposes about whether an adverse event or suspected adverse reaction is "life-threatening" or "serious" be based on the opinion of either the investigator or sponsor. FDA had proposed this revision for the definition of "life-threatening SADRs," and the agency decided that the determination about whether an adverse event or suspected adverse reaction is "serious" is comparable to the determination of whether it is life-threatening. Therefore, FDA revised the definition "serious adverse event or serious suspected adverse reaction" to specify that the determination of seriousness be based on the opinion of either the investigator or sponsor. In addition, FDA eliminated the definition of "disability" as a separate term and includes the meaning of the term in the definition of "serious adverse event or serious suspected adverse reaction."

Third, the final rule makes clear what adverse events or suspected adverse reactions are considered unexpected. The proposed definition of "unexpected SADR" included the following sentence from the then-current definition for "unexpected adverse drug experience" (with minor clarification): "'Unexpected' as used in this definition, refers to an SADR that has not been previously observed (e.g., in the investigator brochure); it does not refer to an SADR that might be anticipated from the pharmacological properties of the drug product." To this clarification, FDA proposed to add the following new sentence: "SADRs that are mentioned in the investigator's brochure as occurring with a class of drugs but not specifically mentioned as occurring with the particular drug are considered unexpected." In this final rule, FDA combined these proposed sentences to read as follows: "'Unexpected,' as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation." This revision makes clear that adverse events that have not been previously observed with the drug under investigation, but are predicted to occur based on the class of the drug or pharmacological properties of the drug are considered "unexpected" for reporting purposes.

B. Review of Safety Information

The final rule clarifies what safety information must be reviewed under § 312.32(b). The proposal would have required sponsors to review "reports from foreign regulatory authorities that have not been previously reported to FDA by the sponsor." FDA has deleted the phrase "that have not been previously reported to FDA by the sponsor," because it confuses the review with the reporting requirements. FDA expects sponsors to review all information, but to avoid duplicate reporting to the agency. In addition, the final rule clarifies the agency's expectations for analysis of previous, similar reports (§ 312.32(c)(1)).

C. Reporting Requirements

In § 312.32(c), the final rule clarifies how and when to submit IND safety reports to FDA and participating investigators, including the requirement in § 312.32(c)(1)(v) that certain reports be submitted in a narrative format (proposed § 312.32(c)(1)(iii)). It provides examples of the kinds of evidence that suggest a causal relationship between the drug and the adverse event when determining whether a serious and unexpected adverse event qualifies for expedited reporting (§ 312.32(c)(1)(i)). The final rule also requires that sponsors submit expedited reports of findings from clinical studies, epidemiological studies, or pooled analyses of multiple studies that suggest a significant risk in humans (§ 312.32(c)(1)(ii)); findings from animal or in vitro testing that suggests a significant risk in humans (§ 312.32(c)(1)(iii)); and reports of an increased rate of occurrence of serious suspected adverse reactions over that listed in the protocol or investigator brochure (§ 312.32(c)(1))(iv)). The final rule also provides for alternative reporting arrangements (§ 312.32(c)(3)) and provides that study endpoints not be reported except in unusual cases (§ 312.32(c)(5)).

Furthermore, FDA has made it clear in § 312.32(c)(1)(v) that the period of time for submitting additional data requested by the agency is 15 calendar

days (i.e., the same period of time that is allowed for submitting followup information under § 312.32(d)(3)). In addition, the agency revised several provisions to allow for electronic submission of reports. First, in § 312.32(c)(1)(v) "Submission of IND safety reports," FDA renamed and revised proposed § 312.32(c)(1)(iii) "Submission of written reports." Second, FDA revised proposed § 312.32(c)(2) "Telephone and facsimile transmission safety reports" to eliminate the specificity that unexpected fatal or life-threatening reports be submitted only by telephone or facsimile transmission so that other means of rapid communication (e.g., e-mail) may be accepted in the future. FDA also renamed the provision to "Unexpected fatal or life-threatening suspected adverse reaction reports." Last, in § 320.31(d)(3), FDA revised the proposed requirement for submission of IND safety reports and unexpected fatal or life-threatening reports from bioavailability and bioequivalence studies to mirror these revisions.

The final rule allows for alternative reporting arrangements, as provided in former § 312.32(c)(3). However, the agency revised the statement, "FDA may request a sponsor to submit IND safety reports in a format or at a frequency different than that required under this paragraph" by replacing the word "request" with "require" to reflect the existing process. In addition, the final rule clarifies the reporting requirements for clinical investigations of drug products that are marketed in the United States (§ 312.32(c)(4)).

The final rule makes minor editorial changes to § 312.32(d)(2) to clarify the followup reporting requirements. In addition, the agency eliminated the redundant submission requirements for information amendments and annual reports under § 312.32(d)(4) because they are already contained in §§ 312.31 and 312.33.

The final rule clarifies the requirements for investigators to submit reports of serious adverse events to the sponsor and clarifies the requirement for reporting study endpoints that are serious adverse events (§ 312.64(b)).

Finally, the final rule requires that applicants submit to FDA reports of serious adverse events from bioavailability and bioequivalence studies. Proposed § 320.31(d) would have required that these studies be subject to the proposed IND safety reporting requirements, thereby requiring all reports under proposed § 312.32 (e.g., reports of serious and unexpected SADRs, reports of information sufficient to consider product administration changes). FDA has tailored the rule to require only those reports that FDA believes would be most informative (i.e., reports of all serious adverse events). FDA also revised this provision to make it consistent with the final revisions for submission of IND safety reports and reports of any fatal or life-threatening adverse event. The final rule requires that reports must be submitted to the Office of Generic Drugs.

Table 1 of this document identifies the changes from the proposed rule in the IND safety reporting requirements that the agency made in this final rule.

TABLE 1—CHANGES MADE BY THE FINAL RULE FROM THE PROPOSED RULE

21 CFR Section in Final Rule	Description of Change See comment or section of this document (identified in parentheses) for more detailed information regarding the change.
312.32(a) Adverse event	• Added definition for "adverse event" (1)
312.32(a) Life-threatening adverse event or life-threatening suspected adverse reaction	• Made minor editorial revisions for clarity, including language changes to accommodate deletion of "SADR" definition and use of alternative terminology (2)
312.32(a) Serious adverse event or serious suspected adverse reaction	• Changed language to accommodate deletion of "SADR" definition and use of alternative terminology (6) • Incorporated the definition from former § 312.32(a) of "disability" within the definition of "serious" (III.A.2) • Revised so that the seriousness determination is based on the opinion of either the sponsor or investigator (6)
312.32(a) Suspected adverse reaction	• Replaced the term "SADR" with the term "suspected adverse reaction," clarifying the meaning of "reasonable possibility" within the definition (1)
312.32(a) Unexpected adverse event or unexpected suspected adverse reaction	• Revised to make clear that "unexpected" adverse events or suspected adverse reactions include those that may be anticipated from the pharmacological properties of the drug, or that occur with members of the drug class, but that have not previously been observed with the drug under investigation (8)
312.32(b) Review of safety information	• Made minor editorial changes for clarity and deleted the phrase "that have not been previously reported to FDA by the sponsor" (II)
312.32(c)(1) IND safety reports	• Withdrew the proposed requirement for each report of an SADR to contain a minimum data set and to maintain records of efforts to obtain a minimum data set (5, 13, and 14)
312.32(c)(1)(i) Serious and unexpected suspected adverse reactions	• Clarified agency's expectation for analysis of previous, similar reports or any other relevant information (16) • Withdrew the requirement that the causality assessment be based on the opinion of the investigator or the sponsor (15) • Provided examples of the types of evidence that suggest a causal relationship between the drug and the adverse event (18 to 21)
312.32(c)(1)(ii) Findings from other studies	• Revised proposed reports of "Information sufficient to consider product administration changes" to clarify agency expectations of reports from clinical studies, epidemiological studies or pooled analyses of multiple studies that suggest a significant risk in humans (23 to 25)

TABLE 1—CHANGES MADE BY THE FINAL RULE FROM THE PROPOSED RULE—Continued

21 CFR Section in Final Rule	Description of Change See comment or section of this document (identified in parentheses) for more detailed information regarding the change.
312.32(c)(1)(iii) Findings from animal or in vitro testing	• Revised proposed reports of "Information sufficient to consider product administration changes" to clarify agency expectations of reports from animal or in vitro testing that suggests a significant risk in humans (26 to 29)
312.32(c)(1)(iv) Increased rate of occurrence of serious suspected adverse reactions	• Added the requirement for reports of any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure (32)
312.32(c)(1)(v) Submission of IND safety reports	• Revised to allow for electronic submission of IND safety reports and clarified time period for reporting additional data or information requested by FDA (II)
312.32(c)(2) Unexpected fatal or life-threatening suspected adverse reaction reports	• Revised to eliminate the specificity that unexpected fatal or life-threatening suspected adverse reaction reports be submitted only by telephone or facsimile transmission and renamed the requirement (II)
312.32(c)(3) Reporting format or frequency	• Replaced "request" with "require" (20)
312.32(c)(4) Investigations of marketed drugs	• Clarified requirements for investigations of marketed drugs (31)
312.32(c)(5) Reporting study endpoints	• Added requirement that study endpoints (e.g., mortality or major morbidity) must be reported according to the protocol instead of as IND safety reports except when there is evidence suggesting a causal relationship between the drug and the event (19 and 21)
312.32(d) Followup	• Deleted provision that required safety information to be submitted in an information amendment or annual report and made minor editorial changes for clarity (III.K)
312.64(b) Investigator reports	• Clarified requirements for investigator reports (35 and 36)
320.31(d) Applicability of requirements regarding an "Investigational New Drug Application"	• Revised to require that persons conducting bioavailability and bioequivalence studies report all serious adverse events (II) • Revised to make consistent with requirements for submission of IND safety reports and reports of any fatal or life-threatening adverse event (II)

III. Comments on the Proposed Rule

The agency received 110 comments in the docket for the March 14, 2003, proposed rule on premarket and postmarket safety reporting revisions. Comments were received from prescription and nonprescription drug manufacturers and related companies; trade organizations representing drug manufacturers and other interested parties; blood banks and transfusion facilities; international organizations and non-U.S. agencies; professional associations and organizations; consultants; contract research organizations; academic institutions; health care and consumer advocacy organizations, individual physicians, pharmacists, and consumers; and others.

To make it easier to identify comments and our responses, the word "Comment," in parentheses, appears before the comment's description, and the word "Response," in parentheses, appears before our response. We have numbered each comment to help distinguish between different comments. Similar comments are grouped together under the same number. The number assigned to each comment is purely for organizational purposes and does not signify the comment's value or importance or the order in which it was received. Comments addressing the proposed requirements for IND safety reporting and bioavailability and bioequivalence studies and the agency's responses follow:

A. Definitions—Proposed § 312.32(a)

1. Suspected Adverse Drug Reaction (SADR)

FDA proposed to add the term "suspected adverse drug reaction (SADR)" and define the term as follows: "A noxious and unintended response to any dose of a drug product for which there is a reasonable possibility that the product caused the response. In this definition, the phrase 'a reasonable possibility' means that the relationship cannot be ruled out."

(Comment 1) Nearly all of the comments overwhelmingly opposed the agency adopting the proposed definition of SADR and strongly encouraged the agency to abandon the proposed definition for many reasons, including the following:

• Many comments did not agree that "reasonable possibility" should be defined as "the relationship cannot be ruled out." Most comments stated that this interpretation makes the definition overly broad and will lead to reporting almost every serious, unexpected adverse event because no event could ever be completely ruled out.

• Many comments stated that although the proposed definition was similar to the definition contained in the ICH E2A guidance, the agency's interpretation was inconsistent with the guidance. The ICH E2A guidance makes clear that a causality assessment is required for clinical investigations and that a "reasonable causal relationship" is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship. The comments expressed concern that the agency's interpretation of "reasonable possibility" would lead to inconsistencies in globally conducted studies and reports.

• Many comments asserted that the significantly increased numbers of expedited reports that could result from the proposed definition might dilute real safety signals, making them harder to detect. The lengthy in depth investigations needed to rule out the increased number of false positive associations would take away resources from other safety surveillance efforts and potentially lead to a delay in identification of real signals.

• Several comments expressed concern that the proposed definition would have a negative impact on the conduct of clinical trials. In addition to sharply increasing the number of reports of cases from clinical trials that would need to be sent to FDA in an expedited manner, sponsors and investigators would have to break the blind for nearly all subjects with serious, unexpected SADRs because the relationship between drug and the event could not definitively be ruled out. Increased unblinding would compromise the integrity of well-regulated clinical investigations, lead to fewer patients completing a trial, necessitate larger patient enrollment, and lengthen the timeline for new product development, possibly leading to higher costs for marketed drugs. One comment expressed concern that, to minimize unblinding, studies would be designed to exclude patients with serious medical conditions who are likely to experience serious adverse events during the study period, thereby limiting the applicability of study results.

Many comments also stated that the proposed definition would result in significant increases in meaningless individual expedited reports being sent to already overburdened IRBs and investigators. The comments pointed out that an unintended effect of the increase in volume of reports may be to reduce an investigator's and IRB's vigilance in detecting adverse events.

• Several comments expressed concern that the proposed definition would dilute the utility of drug product labeling because many more events would be regarded as "drug related" even though the likelihood of a true causal relationship is minimal.

• Several comments stated that the "S" abbreviation for "suspected" in SADR could be confused with the "S" abbreviation for "serious" in SAE (serious adverse event).

The majority of the comments recommended that reporting adverse events from clinical trials should be based on a scientific or medical judgment that there is a possible causal relationship between the drug and the event, rather than simply being unable to unequivocally exclude a drug's role. The comments suggested several alternatives to the agency's proposed definition, including the following:

• Several comments recommended that the definition of an adverse reaction encompass all of the concepts presented within the ICH E2A guidance, which are supported by CIOMS and presented in the European Union Clinical Trial Directive. Comments recommended that the definition of reasonable possibility be technically consistent with the ICH E2A guidance definition and clearly delineate the concept of "reasonable causal relationship" as conveying in general that there are facts (evidence) or arguments to suggest a causal relationship.

• Some comments supported retaining FDA's former definition of "associated with the use of the drug" as "there is a reasonable possibility that the experience may have been caused by the drug."

Three comments supported adopting the proposed definition because they considered it an inclusive, conservative approach to adverse event reporting.

(Response) Based on the comments, and on review of definitions and terminology used in the ICH E2A guidance and in former § 312.32, the agency has decided not to adopt the proposed definition for "suspected adverse drug reaction (SADR)." The agency agrees with the comments stating that there should be a causality assessment applied and that the threshold for reporting should be that there is a "reasonable possibility" that the drug caused the adverse event. The agency also believes that it is important to use definitions that are clear and consistent, and in harmony with those used internationally.

The agency believes that the comments raised legitimate concerns that the proposed definition was too broad and could have a negative impact on clinical trials, IRBs, investigators, signal detection, and drug labeling. Instead of adopting the proposed definition, the agency has adopted the terms for "adverse event" and "suspected adverse reaction" in the definition section of this final rule, which addresses these concerns. The definitions of these terms should contribute to harmonization of safety reporting to regulatory authorities worldwide because they are consistent with the concepts and definitions adopted by the ICH E2A guidance and CIOMS. The terms are defined as follows:

• "Adverse event" means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. (For the purposes of this definition, "untoward" means unfavorable, negative, or harmful).

"Suspected adverse reaction" means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

These definitions reflect the varying degrees of certainty that are part of a causality assessment. For example:

• An adverse event (also referred to as an "adverse experience") is any event observed or reported that is associated with the use of the drug, without regard to causality.

• A suspected adverse reaction is a subset of all adverse events in which there is a reasonable possibility that the drug caused the event.

• An adverse reaction, described within the definition, is a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

With this change from the proposed definition, the basis that the agency has established for assessing the degree of certainty about causality between a drug and an adverse event for the purposes of expedited IND safety reporting has not changed from former § 312.32(c). The sponsor must continue to evaluate the evidence and use its judgment to determine whether an adverse event meets the definition of suspected adverse reaction and qualifies for expedited reporting under § 312.32(c). The agency has also clarified the requirements for reporting a serious and unexpected suspected adverse reaction under § 312.32(c)(1)(i) to assist sponsors with making this determination (see Comment 18 of this document).

Finally, the agency has concluded that abbreviations are potentially confusing (e.g., the "S" abbreviation for "suspected" in SADR could be mistaken for an abbreviation of the term "serious"). Although the agency has retained the term "suspected" in "suspected adverse reaction," our preferred approach is to avoid use of any abbreviation (e.g., "SAR" for "suspected adverse reaction"). The agency believes that sponsors are familiar with the term "suspected" and its use by the European Commission and CIOMS (e.g., the acronym "SUSAR" means "suspected, unexpected, serious adverse reaction" in guidance documents and working group reports (for example, see Ref. 1)).

Because the agency is not adopting the proposed definition of "suspected adverse drug reaction (SADR)," other proposed definitions (e.g., "serious SADR," "life-threatening SADR") and requirements that used this terminology have been revised in this final rule to use the terms "adverse event" or "suspected adverse reaction" as appropriate.

2. Disability

The proposed rule included a definition of the term "disability" to mean a substantial disruption of a person's ability to conduct normal life functions. Because the term "disability" appeared only within the definition of "serious SADR" in the proposed rule, the agency eliminated the definition of "disability" as a separate term in this final rule. Instead, the agency revised the definition of "serious adverse event or serious suspected adverse reaction" in this final rule to incorporate the definition of "disability" by replacing the phrase "a persistent or significant disability/incapacity" with "a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions." Thus, in the final rule, the term disability is replaced by the proposed definition in the one place where it appeared, and the definition itself has been deleted.

3. Life-Threatening Suspected Adverse Drug Reaction (SADR)

FDA proposed the term "life-threatening suspected adverse drug reaction (SADR)" to mean any SADR that, in the view of the investigator or sponsor, places the patient or subject at immediate risk of death from the SADR as it occurred. It does not include an SADR that, had it occurred in a more severe form, might have caused death.

(Comment 2) Several comments agreed with FDA's proposal to add the term "or sponsor" to the definition of life-threatening SADR. SADRs would be reported as life-threatening if either the investigator or sponsor considered them to be life-threatening. However, several comments expressed concern with FDA's proposal. The comments stated that a trained investigator is most qualified to make the sometimes subjective assessment of whether an event is life-threatening and that this determination often is best made by the health-care professional or the reporter who is in direct contact with the patient. These comments also stated that sponsors may exercise medical and scientific judgment in deciding whether expedited reporting is appropriate. One comment stated that allowing a sponsor to determine severity would change the nature of the assessment and result in increased reporting of events assessed by those with often incomplete information. One comment pointed out that FDA's rationale for expanding the role of the sponsor is not supported by the quote from the ICH E2A guidance in the preamble to the proposed rule (68 FR 12406 at 12419) because the ICH E2A guidance quote refers to causality assessment, not assessment of seriousness.

(Response) The agency agrees with the comments that support expanding this definition to include reporting of an adverse event as life-threatening if either the investigator or the sponsor considers it to be life-threatening. The agency believes that, in some cases, the sponsor may not agree with the investigator's assessment that an adverse event does not qualify as life-threatening. In such cases, because these events are critically important for the identification of significant safety problems, the agency believes that broadening the definition to allow sponsors to also make this assessment is prudent and appropriate. While the agency agrees with the comment that pointed out that the preamble to the proposed rule misinterpreted the quote from the ICH E2A guidance, we nonetheless believe that the revision to the definition is consistent with the overall intent of the ICH E2A guidance.

(Comment 3) Several comments disagreed with the agency's position articulated in the preamble to the proposed rule that reasons for any differences of opinion between the investigator and sponsor regarding a determination that an SADR is life-threatening would be included in the IND safety report (68 FR 12406 at 12419). The comments argued that this adds no value and is not appropriate or necessary in all cases. In addition, comments stated that obtaining the investigator's view when he or she deems the event non-life-threatening would be difficult.

(Response) The agency agrees that reasons for differences of opinion between the sponsor and investigator are not always important and, therefore, not necessary to include in the IND safety report in all cases. Therefore, in this final rule, the agency does not require including the reasons for differences of opinion in the IND safety report. However, it is important that any adverse event or suspected adverse reaction considered life-threatening by either the sponsor or the investigator be reported as such.

(Comment 4) Some comments suggested that FDA clarify the definition of life-threatening to take into account the role of other study staff making safety observations. The comments suggested that the definition be clarified to state that investigators or sponsors must evaluate information communicated to them or recorded by their qualified staff or agents and transmit reportable information to the sponsor or FDA. One comment recommended that the definition be modified to include contractors as well as sponsors.

(Response) The agency does not agree that the recommended revisions to the definition are necessary because taking the observations of staff into account is inherent in the obligations of the investigator. Any qualified study staff could make pertinent safety observations, and it is the investigator's responsibility in supervising the conduct of the clinical investigation (see §§ 312.53 and 312.60) to report adverse experiences to the sponsor in accordance with § 312.64. Further information on the supervisory responsibilities of investigators can be obtained in the agency's guidance for industry entitled "Investigator Responsibilities: Protecting the Rights, Safety, and Welfare of Study Subjects" (74 FR 55052, October 26, 2009).[2] The agency does not believe that it is necessary to change the definition to include contractors because, under § 312.52, a contract research organization that assumes any obligation of a sponsor must comply with the applicable regulation.

4. Minimum Data Set

Under § 312.32(a), FDA proposed the term "minimum data set" to mean that "the report includes an identifiable patient, an identifiable reporter, a suspect drug product, and an SADR."

(Comment 5) Two comments requested further clarification regarding the meaning of "identifiable" with respect to the kind and amount of information needed to meet the criteria for an "identifiable patient" and "identifiable reporter." One comment questioned whether patient characteristics, such as age or gender, would be adequate, or if the ability to contact the patient is necessary.

(Response) As discussed in comments 13 and 14 of this document, because the four elements of the minimum data set are generally readily available in the clinical trial setting, the agency has determined that the definition and the requirement are unnecessary and has decided not to require a minimum data set for IND safety reports as proposed in § 312.32(c). Because the agency is not adopting this definition in the IND safety reporting requirements, the comments requesting clarification about

[2] Draft and final guidances for the Center for Drug Evaluation and Research (CDER)-related information are posted on the Internet at *http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm*. The Center for Biologics Evaluation and Research (CBER)-related information is posted at *http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm* (21 U.S.C. 371(h), 21 CFR 10.115).

the elements of the definition are no longer relevant.

5. Serious SADR

FDA proposed to define "serious SADR" in the same way as the then-current definition of "serious adverse drug experience" under § 312.32(a) as follows: "Serious SADR means any SADR that results in any of the following outcomes: Death, a life-threatening SADR, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious SADR when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse."

(Comment 6) One comment suggested that the definition of "serious SADR" be revised to expressly allow the sponsor to determine if an adverse event is serious, in the absence of a reporter's assessment of seriousness.

(Response) For reasons similar to those stated in Comment 2 of this document (definition of life-threatening), the agency agrees that the definition of "serious adverse event or serious suspected adverse reaction" should be revised to allow the determination that an adverse event or suspected adverse reaction is "serious" if either the investigator or sponsor considers it serious. Therefore, the agency has revised this definition to add the phrase "in the view of either the investigator or sponsor."

6. Unexpected SADR

FDA proposed that the definition of "unexpected SADR" be the same as the then-current definition for "unexpected adverse drug experience" under § 312.32(a), except that the following sentence was added to make clear which SADRs are considered unexpected: "SADRs that are mentioned in the investigator's brochure as occurring with a class of drugs but not specifically mentioned as occurring with the particular drug are considered unexpected."

(Comment 7) One comment stated that in the proposed definition, the "severity" standard is vague, leaving the determination of "expectedness" to the investigator's judgment.

(Response) Unless a sponsor-investigator is responsible for the clinical trial, the sponsor, rather than the investigator, generally determines if a suspected adverse reaction is unexpected for reporting purposes. However, the agency acknowledges that judgment is needed to decide if the severity of a suspected adverse reaction is greater than described in the investigator brochure. The definition of "unexpected adverse event or unexpected suspected adverse reaction" in the final rule includes an example of a suspected adverse reaction that would be considered unexpected by virtue of its greater severity than other suspected adverse reactions mentioned in the investigator brochure (i.e., hepatic necrosis would be considered unexpected where the investigator brochure includes elevated hepatic enzymes or hepatitis).

(Comment 8) Another comment recommended that FDA provide guidance on what should be considered "expected" for regulatory reporting purposes, in particular, what safety information to include in the investigator brochure and what subset of such information would be considered "expected" (i.e., only those for which a causal relationship is suspected, reasonably established, or inferred based on evidence). Some comments stated that if the basis for evaluating expectedness is that an event is listed in the investigator's brochure, sponsors may add long lists of adverse events, thereby delaying important safety reports from being submitted to FDA. One comment recommended that FDA require that, until the applicable reference safety information document is officially updated (e.g., reprinted and distributed) to include a new serious, suspected adverse reaction (thereby making it expected), all subsequent reports of similar serious adverse drug reactions be submitted expeditiously as an IND safety report. Another comment suggested adopting use of the Developmental Core Safety Information (DCSI) document, proposed by a CIOMS Working Group, as the reference for "expectedness" instead of the investigator brochure because the DCSI document contains only those adverse events that, after careful analysis are believed by the company to be likely related to the drug (Refs. 2 and 3).

(Response) The purpose of the investigator brochure is to provide the investigator with information (clinical and nonclinical) about the investigational drug that is relevant to study of the drug in human subjects. The investigator brochure should include the information that is important for the investigator, who is administering the drug to human subjects, to know and understand. The investigator brochure is required to include information about the drug substance and formulation, pharmacological and toxicological effects of the drug in animals (and in humans, if known), pharmacokinetics and biological disposition of the drug in animals (and in humans, if known), information relating to safety and effectiveness in humans obtained from prior clinical studies, and information about possible risks and side effects to be anticipated on the basis of prior experience with the drug under investigation or with related drugs, and precautions or special monitoring to be done as part of the investigational use of the drug (see § 312.23(a)(5)).

In general, the investigator brochure lists those adverse events that have been observed with the investigational drug and for which a causal relationship with the drug is suspected or confirmed. It is not appropriate for sponsors to add long lists of adverse events that are unlikely to have been caused by the drug to the investigator brochure because such lists could dilute the importance of clinically meaningful risk information and as a result, may put subjects at risk. The sponsor needs to exercise judgment when deciding if the threshold has been reached for adding a newly observed adverse event to the investigator brochure. This decision usually depends on the strength of the evidence from individual or multiple cases and previous knowledge about the drug or drug class. In some cases, the threshold for including an adverse event may be lower if it could result in a significant adverse outcome for trial participants.

The investigator brochure describes adverse events that may be predicted to occur based on the pharmacological properties of the drug. For reporting purposes, if an adverse event occurs that has not previously been observed with the drug under investigation, the event is considered "unexpected." To make clear that such predicted adverse events are considered "unexpected," the final rule revises the proposed definition of "unexpected" to state explicitly that the term also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

The agency expects the sponsor to update the investigator brochure on an ongoing basis with new important safety information. However, the agency agrees with the comment that, until the investigator brochure and other applicable reference safety information are updated to include a new serious, suspected adverse reaction, subsequent reports of similar serious, suspected adverse reactions must be submitted expeditiously in IND safety reports.

Finally, sponsors submit and the agency accepts a variety of formats for the investigator brochure. For this reason, we are not formally adopting use of the DCSI document in this final rule. However, we agree that a sponsor could incorporate a document such as the DCSI into the investigator brochure for use as the reference for "expectedness" for reporting purposes if the DCSI contains the required safety information about the investigational drug.

B. Review of Safety Information—Proposed § 312.32(b)

IND safety reporting regulations in former § 312.32(b) required that sponsors promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from any source, foreign or domestic. Examples of potential sources of information in the former regulation included information derived from any clinical or epidemiological investigations, animal investigations, commercial marketing experience, reports in the scientific literature, as well as unpublished scientific papers, and reports from foreign regulatory authorities that had not been previously reported to FDA by the sponsor. Proposed § 312.32(b) would have amended this requirement to include in vitro studies as another example of a potential source of information and to clarify that "reports from commercial marketing experience" is intended to apply only to reports from foreign commercial marketing experience for drugs that are not marketed in the United States. As proposed, reports from IND studies of drugs that are marketed in the United States would be required to be reported as described under § 312.32(c)(4), if applicable.

(Comment 9) One comment stated that reportable information can come from a wider variety of media or sources than those listed in the proposed rule. The comment maintained that investigators or sponsors participating in public or private meetings or conferences can learn of reportable events from colleagues or other professionals. The comment recommended that the list of potential sources of reportable information include such alternative sources.

(Response) The sponsor is required to "promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from foreign or domestic sources, including information derived from any clinical or epidemiological investigations, animal or in vitro studies * * *" (emphasis added). The sources listed in the requirement are not all inclusive, but represent examples of the variety of sources that may yield safety information. Therefore, the agency agrees that reportable information can come from sources other than those listed in § 312.32(b) and that one such source could be from public or private meetings. However, the agency does not believe that it is necessary to amend the requirement to provide additional examples.

(Comment 10) One comment agreed with the clarification that reporting from commercial marketing experience applies only to foreign commercial marketing experience for drugs that are not marketed in the United States. The comment requested that FDA further make it clear that expedited reporting under § 312.32 is not required for reports from foreign commercial marketing experience for a different formulation of the same active moiety as a drug product that is lawfully marketed in the United States and that those reports should be submitted to the most appropriate new drug application (NDA) for the active moiety.

(Response) As described further in Comment 31 of this document, IND safety reports are required under § 312.32(c)(4) for suspected adverse reactions observed in clinical studies that are being conducted under an IND for a drug marketed or approved in the United States. In general, an expedited report from domestic or foreign commercial marketing experience for a drug lawfully marketed in the United States would not be submitted to the IND, but instead, must be submitted in accordance with the relevant postmarketing reporting requirements (e.g., §§ 310.305, 314.80, and 600.80). Similarly, a report of a suspected adverse reaction from foreign marketing experience for a different formulation of the drug product (same active moiety) that is lawfully marketed in the United States must be submitted in accordance with the relevant postmarketing reporting requirements.

(Comment 11) One comment agreed with the proposal to add in vitro studies to the list of information that should be reviewed by the sponsor in its ongoing assessment of the safety of an investigational drug. Some comments stated that it would be helpful if FDA could provide examples, in addition to carcinogenicity, mutagenicity and teratogenicity, of when safety data from in vitro studies would yield relevant, important information that should be reviewed for IND reporting purposes.

(Response) Data from in vitro microsusceptibility, drug interaction, or genotoxicity studies are examples of other data from in vitro studies that may yield important safety information.

(Comment 12) One comment expressed concern that once a sponsor provides FDA with the animal and in vitro studies, emails, and reports from foreign regulatory authorities and any other information it reviewed in determining whether to report safety information, FDA may have to make the information publicly available under the Freedom of Information Act (FOIA). The comment stated that, before implementing the requirement, FDA should explain why these additional data are needed and how they will be handled for FOIA purposes. The comment requested that the requirement be withdrawn.

(Response) The agency uses the safety information submitted by the sponsor, from any source, to continually monitor and evaluate the safety of the drug. Data and information in an IND are disclosed consistent with applicable statutes and regulations. The requirements under § 312.130 describe the availability for public disclosure of data and information in an IND. The minor clarifications made to these requirements do not change these protections against public disclosure. Therefore, the agency declines to withdraw the requirement as requested by the comment.

C. IND Safety Reports (Requirement for Minimum Data Set)—Proposed § 312.32(c)

FDA proposed to amend § 312.32(c) to require that sponsors must not submit an individual case safety report for an SADR if the report does not contain a minimum data set, but instead must maintain records of any information received or otherwise obtained for the SADR along with a record of its efforts to obtain a minimum data set. In the preamble to the proposed rule, the agency stated that sponsors should include in any written IND safety reports subsequently filed with FDA a chronological history of their efforts to acquire the minimum data set if there is a delay in obtaining the information, but that it was not necessary to include the chronological history in IND safety reports sent to investigators (68 FR

12406 at 12424). In addition, FDA proposed in § 312.32(c)(1)(i) that a sponsor must submit an IND safety report within 15 calendar days after receipt by the sponsor of the minimum data set for the SADR.

As noted in Comment 5 of this document, the agency has reconsidered the proposed requirement under § 312.32(c) that would have required sponsors to only submit an individual case safety report for an SADR if the report contained a minimum data set. Most IND safety reports are derived from observations from clinical trials. In the setting of a clinical trial, information is collected in a controlled environment where the four elements in the definition of minimum data set, as well as other information needed to evaluate the suspected adverse reaction (e.g., information that would be contained in a narrative report or on FDA Form 3500A), are generally readily available. Accordingly, the agency has revised § 312.32(c)(1) to eliminate the minimum data set language and to require instead that the sponsor submit an IND safety report after it determines that the information qualifies for reporting under § 312.32(c)(1)(i), (c)(1)(ii), (c)(1)(iii), or (c)(1)(iv).

(Comment 13) One comment stated that waiting for collection of all the elements of the minimum data set, especially for determination of causality, could result in a significant delay in reporting to FDA. The comment requested clarification on when the reporting timeclock would start. Another comment requested clarification on whether the date of receipt of the minimum data set for the SADR represents day zero or day one.

(Response) The reporting timeclock starts (i.e., day zero) as soon as the sponsor determines that the information qualifies for reporting under § 312.32(c)(1)(i), (c)(1)(ii), (c)(1)(iii), or (c)(1)(iv). For a serious and unexpected suspected adverse reaction from a clinical trial, this would be the day the sponsor receives information from the clinical investigator. If any information necessary to evaluate and report the suspected adverse reaction is missing or unknown, the sponsor should actively seek such information.

(Comment 14) Several comments stated that including in an IND safety report a chronological history of their efforts to acquire the minimum data set is inconsistent with standards for non-U.S. regulators and the ICH E2A guidance, adds no value, may lead to potential legal risk in the event of litigation, may impede electronic transmission of individual case safety reports, and will become an administrative burden. Some comments suggested that records of efforts to obtain the minimum data set should be maintained within the case record in the sponsor's files, available upon request or during agency inspections. One comment suggested FDA require manufacturers to have procedures in place to acquire a minimum data set. One comment stated that the agency needs to define the minimum requirements for conducting due diligence to avoid variation from sponsor to sponsor. Another comment recommended reinforcing the need for sponsors to conduct followup activities and for FDA to audit industry for compliance. One comment requested clarification on the sponsor's timeframe for maintaining records of its efforts to obtain the minimum data set. One comment pointed out that although FDA stated in the preamble that the chronological history included in the IND safety report would not need to be sent to investigators, this statement creates conflict because sponsors must tell investigators the same information that is reported to FDA.

(Response) The agency agrees with comments that including a chronological history in an IND safety report of efforts to acquire information is not necessary and could be an administrative burden without added value. Accordingly, the proposed requirement for a chronological history has been deleted from § 312.32(c). Under § 312.32(d)(1), sponsors are required to promptly investigate all safety information received, so it is inherent in that requirement that sponsors promptly and diligently attempt to obtain the information necessary for evaluating a suspected adverse reaction. If critical information is missing or unknown, the sponsor should actively seek the information. The regulations do not include specific procedures for conducting or documenting due diligence activities because the agency recognizes that there is more than one approach that would be appropriate, depending on the situation.

Similarly, because the minimum data set requirement is no longer included, the agency is not adopting the proposed requirement in § 312.32(c) to maintain records of any information received or otherwise obtained for the SADR when the sponsor does not have a reportable minimum data set. The agency notes that sponsors are required under § 312.57(c) to retain records and reports required under part 312 (including safety information received by the sponsor) for 2 years after a marketing application is approved for the drug or, if an application is not approved for the drug, until 2 years after shipment and delivery of the drug for an investigational use is discontinued and FDA has been so notified. The agency may audit these records as part of its inspection process.

D. Serious and Unexpected SADR—Proposed § 312.32(c)(1)(i)

In proposed § 312.32(c)(1)(i), FDA proposed that the sponsor must notify FDA and all participating investigators in a written IND safety report of any SADR that, based on the opinion of the investigator or sponsor, is both serious and unexpected, as soon as possible, but in no case later than 15 calendar days after receipt by the sponsor of the minimum data set for the serious, unexpected SADR. In addition, FDA proposed that the sponsor must identify all safety reports previously filed with the IND concerning a similar SADR, and must analyze the significance of the SADR in light of the previous, similar reports.

(Comment 15) One comment agreed with the proposal that the assessment of whether the event is serious or unexpected be based on the opinion of the "investigator or sponsor," while other comments expressed concern. Several comments indicated that investigators should not be required to assess "expectedness." One comment stated that "expectednessx" is a regulatory definition that would be difficult for an investigator to apply in a consistent manner. Another comment suggested replacing the proposed language with "any SADR that is serious based on the opinion of the investigator or sponsor and unexpected."

(Response) The agency agrees that, in contrast to the assessments of whether an adverse event or suspected adverse reaction is "serious" and "life-threatening," which require medical judgment by the investigator or sponsor, the assessment of whether an adverse event or suspected adverse reaction is "unexpected" in this context refers to a regulatory definition (i.e., not listed in the investigator brochure) that is more appropriately applied by the sponsor. The sponsor is usually in a better position to assess the adverse event information and determine whether the adverse event is "unexpected" for reporting purposes because the sponsor has access to more information (e.g., from all the investigative sites in a multi-center study). Therefore, the agency has revised this proposed requirement by deleting the phrase "based on the opinion of the investigator or sponsor," which leaves this determination to the sponsor.

(Comment 16) Several comments asked for clarification on various aspects of the requirement to identify all safety reports previously filed with the IND concerning a similar SADR and to analyze the significance of the SADR in the context of the previous, similar reports. One comment requested clarification on the meaning of "previously filed with the IND" and whether this should include an analysis of previous similar reports across multiple open INDs or only a single IND. The comment noted that there could be company-sponsored IND studies and investigator-sponsored IND studies ongoing simultaneously, with safety data stored in different places. One comment requested clarification on what constitutes a "similar" SADR and on the meaning of "analyze the significance." This comment noted that companies should already have processes and procedures in place to periodically review and analyze safety data to detect "signals," and asked whether FDA expects an "analysis" for postmarketing study reports filed to the IND or all reports for the product, including postmarketing spontaneous reports. The comment suggested that FDA remove this requirement for both IND and postmarketing studies, since for IND studies, companies should already be performing these analyses and updating their investigator brochures with significant new safety information, and for postmarketing studies, analyses of all adverse events are being performed in the periodic safety update report (PSUR).

(Response) The agency expects the analysis of the significance of the suspected adverse reaction in the context of similar reports to include all INDs held by the sponsor and any other relevant information of which the sponsor is aware. To make this clear, the agency revised the provision in final § 312.32(c)(1) to require that in each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction, and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information.

The agency declines to withdraw the requirement as suggested by the comment because we consider this information to be critical for the ongoing evaluation of the investigational drug's safety. Because this is not a new requirement (see former § 312.32(c)(1)(ii)), the agency agrees that companies should have processes in place to periodically review and analyze their safety data and update their investigator brochures with significant new safety information. This analysis should include an evaluation of the suspected adverse reaction in the context of other related reports or adverse events, including those that may have occurred in postmarketing studies.

(Comment 17) One comment asked whether the IND safety report should be sent only to investigators participating in company-sponsored studies or to studies conducted under all open INDs for the product. One comment requested that FDA clarify its expectations for cross-reporting to investigators participating in different trials under the same IND or different INDs with the same active moiety. One comment asked if followup IND safety reports containing only minor refinements are to be sent to FDA and all investigators who received the initial safety report or only to FDA.

(Response) The sponsor must report to any participating investigators under all open INDs, including those held by the sponsor and those to which the sponsor provides the investigational drug (investigator-sponsored). To make this clear, the agency revised the provision in § 312.32(c)(1) to require that a sponsor notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting under § 312.32(c)(1)(i), (c)(1)(ii), (c)(1)(iii), or (c)(1)(iv).

Followup reports should be sent to investigators to inform and update them about an important suspected adverse reaction if it significantly affects the care of the subjects or conduct of the study. Minor refinements that do not significantly affect care of subjects or conduct of the study need to be sent to FDA but need not be sent to investigators. Such information may be communicated to investigators in a routine update of the investigator brochure.

(Comment 18) As stated in Comment 1 of this document, there were many comments opposed to FDA's proposed SADR definition, some of which recommended against adopting the proposed SADR definition, and instead, urged FDA to clarify the types of evidence that suggest there is a reasonable possibility that a drug product caused the adverse event.

(Response) Before submitting an IND safety report under § 312.32(c)(1)(i), the sponsor must determine that the event: (1) Is serious, (2) is unexpected, and (3) meets the definition of "suspected adverse reaction" in § 312.32(a) (i.e., that there is a "reasonable possibility" that the drug caused the event). These criteria have not changed from former § 312.32(c)(1)(i)(A). Making this determination will always require judgment based on the best available information.

Currently, sponsors often report in an expedited manner serious adverse events that may be due to the underlying disease or that occur commonly in the study population, even when there is little reason to believe that the drug caused the event. Such reports are generally uninformative and, therefore, do not meaningfully contribute to the developing safety profile of the drug. The agency believes that clarifying what evidence suggests a causal relationship will increase the likelihood that information reported to FDA will meaningfully contribute to the developing safety profile of the product and improve the overall quality of safety reporting.

Therefore, to assist sponsors with determining whether an adverse event meets the definition of suspected adverse reaction, the agency revised the proposed requirement under § 312.32(c)(1)(i) to make it clear that sponsors are to report to FDA and all participating investigators only if there is evidence to suggest a causal relationship between the drug and the adverse event. Final § 312.32(c)(1)(i) also provides the following examples:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome).
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture).
- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

E. Alternative Reporting Arrangements

In the preamble to the proposed rule, FDA acknowledged that the proposed

definition of SADR (which defined "reasonable possibility" to mean that the causal relationship between a product and a response to the product cannot be ruled out) may result in submission of numerous safety reports to the agency for which the reported SADR is not informative as a single report because it is very likely to have been a consequence of the patient's disease. FDA invited comment on use of alternative reporting methods that would minimize overreporting of uninformative events and assure submission of meaningful reports of unexpected events. For example, one such alternative would be to include in study protocols or other documentation a list of known consequences of the disease that would not be submitted to FDA in an expedited manner as individual case safety reports (e.g., events that are endpoints of the study) (68 FR 12406 at 12418).

(Comment 19) Some comments agreed with the agency's suggestion that protocols could be written to exclude specific disease-related events from expedited reporting if these events are study endpoints. Other comments expressed concern that alternative reporting methods would not have the intended effect of reducing overreporting and could exacerbate problems with the proposed SADR definition of reasonable possibility in which the causal relationship "cannot be ruled out." They argued that effectively eliminating clinical judgment in reporting coupled with an ad hoc exemption mechanism would lead to different standards across clinical programs, between different sponsors of studies, and across FDA review divisions. These comments further pointed out that negotiating and managing exemptions to expedited reporting would place a significant burden on FDA and companies and would necessitate the creation of an FDA structure and process to ensure consistency across products. While many of these comments recommended against finalizing the proposed definition, others suggested alternatives (e.g., waiver provisions) to alleviate overreporting caused by the proposed definition. One comment recommended that approaches to minimize overreporting only be considered for late stage development (i.e., Phase 3 and 4 studies). One comment recommended that FDA mandate expanded reporting for clinical trials only for those companies that have had documented poor performance in the past or for clinical trials once a study or design has been identified as posing a potential or unforeseen risk to participants.

(Response) As previously described in the response to Comment 1 of this document, the agency is not adopting the proposed SADR definition and, instead, is adopting a definition of "suspected adverse reaction" that relies on clinical judgment to determine if there is a reasonable possibility that the drug caused the event. While FDA believes this definition addresses many of the concerns about overreporting, the agency agrees with the comments that stated that protocols could be written to exclude from expedited reporting specific disease-related events that are study endpoints. The agency does not believe that it is appropriate to report study endpoints as IND safety reports for trials that are designed to evaluate the effect of the drug on disease-related mortality or morbidity. Therefore, the agency added the requirement at § 312.32(c)(5) that study endpoints (e.g., mortality or major morbidity) must be reported to FDA by the sponsor as described in the protocol and ordinarily would not be reported under § 312.32(c). However, if a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis), the event must be reported under § 312.32(c)(1)(i) as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (e.g., all-cause mortality). FDA does not believe that this requirement will pose an additional burden on sponsors or the agency because sponsors of large outcome trials are accustomed to describing in the protocol how mortality or major morbidity endpoints will be measured and analyzed, and FDA review divisions are accustomed to reviewing such protocols.

The agency does not agree that the safety reporting requirements should be revised, as suggested by the comment, to address specific study or design risks or company compliance. The agency is authorized to require additional reporting or inspection, or to take action, on a case-by-case basis if, for example, such problems expose human subjects to unreasonable and significant risk of illness or injury, or if the sponsor does not comply with the requirements under § 312.32 (see e.g., § 312.42 clinical holds and requests for modifications, § 312.44 termination).

(Comment 20) Several comments supported the use of alternative reporting arrangements for serious adverse events that are not the study endpoints (e.g., known consequences of the underlying disease or condition). These comments recommended that these events not be reported to FDA in an expedited manner as individual case safety reports, but be identified in the study protocol with clear instructions for handling, be monitored by the sponsor, and be reported to the agency if, in aggregate, it appears that the product may be causing an increase in these adverse events. One comment endorsed this type of arrangement because it offers the potential for improvements in protocol design by providing expanded opportunity for sponsors to discuss the "ground rules" for SADR reporting for specific studies with the agency during the protocol design phase. Two comments recommended that FDA make clear to investigators, sponsors, manufacturers, and IRBs that such arrangements are acceptable. One comment stated that allowing this type of alternative reporting arrangement will provide a loophole for industry to underreport adverse events.

(Response) Under former § 312.32(c)(3), sponsors were permitted to propose alternative reporting formats or frequencies for submitting IND safety reports; this requirement has not changed in this final rule. The agency agrees with the comments recommending that at the time of protocol development the sponsor identify the serious adverse events (i.e., known consequences of the disease or those otherwise common in the study population) that it plans not to report individually in an expedited manner but that it will monitor during the course of the trial. FDA encourages use of this process. Should an aggregate analysis indicate that those events occur more frequently in the drug treatment group, the sponsor must then report that information in an IND safety report under § 312.32(c)(1)(i). However, the agency recognizes that it is not possible, nor desirable, to list in the protocol every adverse event that may be anticipated to occur in the study population; the protocol should therefore limit such a list to those events that are common, even in the absence of drug exposure. For example, in a long-term osteoporosis trial in an elderly population, it would be reasonable to list myocardial infarction, but unreasonable to list acute narrow angle glaucoma—an event that can occur in this elderly population, but is relatively rare. In addition, the agency believes that there may be other situations for which alternative reporting arrangements are appropriate based on the clinical circumstances. For example,

the agency may require a sponsor to continue to report expeditiously a medically significant suspected adverse reaction that is listed in the investigator brochure as observed with the drug (i.e., expected) so that its rate can be carefully monitored. The agency may also require an alternative reporting format or frequency for clinical trials once a study or design has been identified as posing a potential or unforeseen risk to participants. In other instances, a sponsor may request that a certain adverse event be submitted in a different format or at a different frequency than required. Section 312.32(c)(3) permits such arrangements. The agency does not agree that allowing alternative reporting formats or frequencies creates loopholes for sponsors to underreport, but believes that such arrangements will lead to greater vigilance since particular adverse events of interest have been identified in advance. The agency is clarifying the language in former § 312.32(c)(3) that stated "FDA may request a sponsor to submit IND safety reports in a format or at a frequency different than that required under this paragraph" by replacing the word "request" with "require" to better reflect the existing process.

F. Unblinding

In the preamble to the proposed rule, FDA noted that reports from blinded clinical studies should have the blind broken to identify the drug product, but that alternative arrangements could be made with FDA for exceptions to breaking the blind for a clinical study in which mortality or serious morbidities are the clinical endpoint of the study. FDA invited comment on whether the blind should also be broken for other serious SADRs that are not the clinical endpoint of the study, but occur at a rate high enough that the overall study blind would be threatened if each such case were individually unblinded (68 FR 12406 at 12420).

(Comment 21) Several comments expressed concern that breaking the blind to identify the suspect drug could potentially bias both the sponsor and investigator, and suggested alternatives to unblinding so that sponsors and investigators could remain blinded. In addition, several comments responded to FDA's request for comment on whether the blind should be broken for serious SADRs that are not the clinical endpoint of the study. One comment stated that for other serious SADRs (e.g., expected), if a safety signal is observed, sponsors are obligated to unblind studies for individual subject cases, but other comments stated that medical management of the subject who experiences the serious SADR does not always require unblinding. One comment stated that the sponsor and FDA should define in advance the nature of such serious SADRs that would not be subject to routine expedited reporting and unblinding. One comment stated that for studies in which alternative arrangements have been made to maintain the blind, FDA should receive interim analyses, disaggregated by group, which might suggest increased overall dangers to those getting the drug.

(Response) The agency believes that the concerns expressed about breaking the blind have been addressed by clarifying the reporting requirements for serious and unexpected suspected adverse reactions (§ 312.32(c)(1)(i)) and for study endpoints (§ 312.32(c)(5)), and the provision permitting alternative reporting arrangements (§ 312.32(c)(3)). In particular, because there should generally be no need to report study endpoints in an IND safety report, unblinding due to such endpoints should typically not occur. In other cases, however, where the serious, unexpected, suspected adverse reaction must be reported expeditiously, the agency expects the blind to be broken. Knowledge of the treatment received may be essential for the medical management of the subject and may provide critical safety information about the drug that could have implications for the ongoing conduct of the trial (e.g., monitoring, informed consent). The agency does not believe that unblinding single or small numbers of informative cases will compromise the integrity of the study. However, if patient safety can be assured without breaking the blind, the agency encourages the sponsor to discuss alternative reporting arrangements with the appropriate FDA review division. Any anticipated alternative arrangements to maintain the blind would need to be described in the protocol, including identification of the serious adverse events that will not be reported on an individual basis and the plan for monitoring and reporting results to FDA.

(Comment 22) Several comments made recommendations on the need for, and role of independent data safety monitoring boards (DSMBs), called Data Monitoring Committees (DMCs) in FDA's guidance for industry entitled "Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees" (71 FR 15421, March 28, 2006) (DMC guidance). One comment stated that an obligation to have an independent DSMB would prevent routine unblinding. Other comments recommended the use of DSMBs that have processes for vetting and reporting adverse reactions to the agency, including monitoring for increases in disease-related complications. One comment recommended that the agency concurrently amend the IRB regulations and guidelines to incorporate a mandate of more frequent review of overall safety data, including a requirement for an independent safety monitoring committee, under predefined circumstances. Another comment urged the agency to require a DSMB for all Phase 3 studies and to also require that sponsors provide DSMB reports to IRBs. One comment said that clarity on the role of the DSMB for Phase 3 and 4 studies when reviewing SADRs could help reduce redundancy of SADR reporting evaluations by IRBs, and allow IRBs to more efficiently focus their attention on local SADRs.

(Response) The agency agrees that DMCs can be useful for monitoring adverse events and preventing routine unblinding in certain trials. A DMC is not required and is not necessary for most studies, particularly those evaluating symptomatic treatments. DMCs are generally associated with a large, randomized multisite trial that is designed to evaluate treatments intended to improve survival or reduce the risk of major morbidity. In that case, the independent DMC would be expected to monitor serious events that are study endpoints and also may assess the rate of other known consequences of the underlying disease or other events that are common in the study population. FDA's DMC guidance also notes another potential use for a DMC. Some sponsors have used a DMC to monitor the overall event rates as the safety database accumulates in ongoing studies (DMC guidance at p. 23). A DMC could periodically analyze and evaluate the aggregated, unblinded events in the entire IND safety database to determine if the drug is the suspected cause. During these analyses, investigators and study participants would remain blinded. FDA's DMC guidance also provides more information on determining the need for and the role of a DMC. In addition, the agency's guidance for industry entitled "Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting—Improving Human Subject Protection" provides recommendations on efficient approaches to meeting the requirements for reporting unanticipated problems to IRBs (74 FR 2599, January 15, 2009).

G. Information Sufficient to Consider Product Administration Changes—Proposed § 312.32(c)(1)(ii)

In addition to requiring sponsors to provide written IND safety reports to FDA and investigators for any serious and unexpected adverse experience, former § 312.32(c)(1)(i) required a written IND safety report for "[a]ny finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity." FDA proposed to revise this requirement to require sponsors to submit a written IND safety report if the sponsor receives information sufficient to consider product administration changes. The proposed rule described information sufficient to consider product administration changes as "information that, based on appropriate medical judgment, might materially influence the benefit-risk assessment of an investigational drug or that would be sufficient to consider changes in either product administration or in the overall conduct of a clinical investigation" (68 FR 12406 at 12476). Examples of the types of information that might give rise to such a report were described as "any significant unanticipated safety finding or data in the aggregate from an in vitro, animal, epidemiological, or clinical study, whether or not conducted under an IND, that suggests a significant human risk, such as reports of mutagenicity, teratogenicity, or carcinogenicity or reports of a lack of efficacy with a drug product used in treating a life-threatening or serious disease" (68 FR 12406 at 12476).

(Comment 23) Several comments maintained that the threshold for submission of this category of IND safety report—information sufficient to consider product administration changes—needs clarification. Some comments stated the "information sufficient to consider product administration changes" is too vague a criterion on which to base a reporting requirement and that "product administration" may have different interpretations in the context of safety. Some comments pointed out that there is ongoing "consideration" of the implications, for product administration, of information that emerges during the conduct of a trial and often, upon consideration, it will be concluded that no changes are needed. Some comments recommended that there be an IND safety report only in the event of a product administration change or other change in the conduct of the investigation. One comment recommended that FDA consider the implications (e.g., potential confusion) of informing investigators about information sufficient to consider product administration changes before a decision has been made about whether to make a change. That comment recommended that only FDA receive the information sufficient to consider product administration changes and that the investigator be notified only in the event of an actual product administration change. Some comments pointed out that the proposed language does not differentiate among the range of possible product administration changes and thus would seem to require an expedited report for minor changes that do not warrant expedited reporting. The comments suggested that there be expedited reporting only in the event of significant product administration changes. One comment stated that information sufficient to consider product administration changes is a reasonable category for an IND safety report. The comment asked that FDA clarify that significant risk to humans is intended to include instances of significant impairment or dysfunction.

(Response) The agency concurs that, as proposed, the requirement may be confusing. In response to comments, the agency has revised the proposed requirement for reporting data or findings from clinical or epidemiological studies to address the concerns about vagueness of terms and criteria that could lead to differences in interpretation. The revised requirement eliminates the association with "product administration changes" and makes clear the types of findings that would trigger the requirement to report under this provision. In addition, the revised requirement also makes clear that the findings from clinical studies that are subject to this requirement are other than those reported under § 312.32(c)(1)(i) (e.g., findings from a drug interaction study). The agency has revised § 312.32(c)(1)(ii) to require the sponsor to report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies (other than those reported under § 312.32(c)(1)(i)),whether or not conducted under an IND and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug. The provision goes on to state that, ordinarily, such a finding would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.

These changes to the proposed requirement also address the comments concerned about potentially prematurely notifying all investigators prior to conclusively determining whether a finding might change the product administration or conduct of the investigation because the sponsor would report to FDA and notify all participating investigators, as required by § 312.32(c)(1), after that determination has been made by the sponsor.

In addition, FDA agrees with the comment that "significant risk in humans" would include instances of significant impairment or dysfunction.

(Comment 24) One comment asked that FDA clarify what is meant by "might materially influence the benefit-risk assessment" (68 FR 12406 at 12476). The comment pointed out that a literal interpretation would require an IND safety report for a finding that is favorable to the benefit-risk assessment as well as a finding that is unfavorable to the benefit-risk assessment, but would have no effect on the clinical use of the drug. Another comment maintained that the term benefit-risk has no clear meaning in the premarket context because efficacy has not been proven, i.e., there is no established benefit for the product being studied.

(Response) The agency agrees that the proposed requirement may be confusing. Therefore, the agency has not included the phrase "might materially influence the benefit-risk assessment" in § 312.32(c)(1)(ii).

(Comment 25) Some comments questioned FDA's intent and otherwise expressed concern about requiring IND safety reports of lack of efficacy for a drug intended to treat a life-threatening or serious disease. One comment pointed out that "lack of efficacy" is rarely used in the clinical trial setting to refer to cases of disease progression or nonresponders. The comment maintained that because of the difficulty in judging lack of efficacy, such reports should be limited to cases in which the investigator has specifically determined that there was lack of efficacy. One comment maintained that the term is incongruous in the clinical trial setting because efficacy of the drug has not been demonstrated. One comment pointed out that the term "lack of efficacy" is not used consistently throughout the proposed rule (i.e., premarket compared to postmarket setting).

(Response) The agency agrees with the comment stating that the term "lack of efficacy" is incongruous in the

clinical trial setting because the effectiveness of the drug has generally not been established. Therefore, the final rule does not include this proposed provision.

(Comment 26) One comment stated that in vitro and animal findings should not be lumped together with clinical findings for purposes of the information sufficient to consider product administration changes IND safety reports because in vitro and animal findings typically are assessed differently than clinical findings. The comment also argued that there is significant variation in the interpretation of the current reporting requirements for nonclinical findings and recommended establishing distinct, well-defined criteria for reporting of nonclinical findings. The comment recommended a separate safety report for animal and in vitro findings with the following criteria: (1) A drug-related finding, (2) an unanticipated finding, and (3) a finding that suggests a serious risk to humans. The comment further maintained that the company's core safety information about the drug should be the basis for determining whether the finding is unanticipated and the term "serious" should be defined, in this context, as suggesting a significant human risk, including, but not limited to, reports of carcinogenicity, mutagenicity, or teratogenicity.

(Response) The agency agrees that the way in which in vitro and animal findings are assessed differs from clinical findings. To make this distinction clear, the agency has revised the proposed requirement to separate reports of findings from nonclinical and clinical studies. Under § 312.32(c)(1)(iii), the sponsor must report any findings from any animal or in vitro testing, whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug, such as reports of mutagenicity, teratogenicity, carcinogenicity, or reports of significant organ toxicity at or near the expected human exposure. The provision states that, ordinarily, any such findings would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.

The revised requirement also eliminates the terms "unanticipated" and "serious." The agency agrees with the comment that an unanticipated, drug-related finding that suggests a significant risk to humans would meet the requirement for reporting.

(Comment 27) Two comments asked FDA to clarify the scope of what is meant by "an animal finding suggestive of significant human safety risk." One comment asked whether there are any animal findings other than carcinogenicity, mutagenicity, or teratogenicity that would be considered a significant human safety risk and whether a finding needs to originate from a reproducible validated controlled model. One comment stated that the final rule should state explicitly that only those findings of carcinogenicity, mutagenicity, or teratogenicity that the sponsor considers suggestive of significant risk to humans should be reported. The comment pointed out that some carcinogenicity, mutagenicity, and teratogenicity findings are known to be species-specific or for other reasons known not to suggest significant potential human risk and thus should not be subject to expedited reporting. Another comment suggested a distinction be made between a nonclinical finding that requires "changes in either product administration or in the overall conduct of a clinical investigation" as opposed to a nonclinical finding that requires information only (e.g., action is limited to a nonurgent update of the investigator brochure and informed consent).

(Response) The requirement has been revised to make it clear that, ordinarily, a finding would be considered suggestive of a significant risk in humans if it results in a safety-related change in the protocol, informed consent, investigator brochure, or other aspects of the overall conduct of the clinical investigation. Nonurgent, routine updates to the investigator brochure and informed consent would not meet the criteria for reporting under this provision and should not be reported in an expedited IND safety report.

The sponsor must determine whether a finding suggests a significant risk in humans in order for the finding to be reportable. Animal findings such as carcinogenicity, mutagenicity or teratogenicity are meant to be examples of the types of findings that could suggest a significant human risk, but there are others that could meet the criteria for reporting. For clarity, the agency added another example in § 312.32(c)(1)(iii) (i.e., reports of significant organ toxicity at or near the expected human exposure). Findings from animal studies do not necessarily need to be replicated to meet the criteria for expedited reporting to FDA. For example, the agency would not expect a long-term carcinogenicity study to be replicated if findings from the original study suggested a significant risk to humans. The validity of the model would be a factor taken into account in evaluating the strength of the evidence of significant risk.

(Comment 28) Many comments expressed concern about in vitro testing alone as a basis for an IND safety report. One comment pointed out that certain types of in vitro findings that are known to be associated with an increased risk of carcinogenicity or mutagenicity are always reported, but other findings are not obviously worthy of reporting. Some comments argued that expanding the scope of expedited reporting to include in vitro testing is not warranted or useful. Some comments maintained that in vitro testing is often exploratory and not validated and thus lends itself to unanticipated findings, but the clinical implications of in vitro testing are often not understood until later when the data can be assessed in light of animal or clinical findings. Given this delay in the interpretability of in vitro findings, the comments asked FDA to clarify when an in vitro finding becomes reportable for purposes of an IND safety report. Some comments argued that the increased reporting burden for in vitro findings would result in large numbers of uninformative reports that would burden FDA and dilute the impact of truly informative safety reports. Some comments also maintained that expanded reporting requirements may deter sponsors from conducting the kinds of in vitro testing that could reduce the number of animal studies needed.

(Response) In response to comments and as stated in Comments 26 and 27, the agency has revised the proposed requirement § 312.32(c)(1)(iii) to make it clear that an in vitro or animal finding is reportable for the purposes of an IND safety report if it suggests a significant risk in humans exposed to the drug. The sponsor would not report an in vitro finding in an expedited report unless it determined that the finding suggests a significant risk in humans.

(Comment 29) Some comments asked FDA to clarify the timeframe for reporting under this requirement, including when in vitro and animal studies become reportable sources of safety information by explaining how "the determination by the sponsor that the information qualifies for reporting under this paragraph" applies to nonclinical findings. One comment suggested that the reporting clock for in vitro and animal findings start on the date the final study report is completed. One comment asked that FDA clarify that the day that the 15-day period begins is day zero and not day one.

(Response) The agency believes that the revisions to this requirement have sufficiently detailed how information qualifies for reporting by providing examples of the outcome of such a finding (i.e., the finding would ordinarily result in a safety-related change in the protocol, informed consent, investigator brochure, or in other aspects of the overall conduct of the clinical investigation). The 15–day reporting clock begins (i.e., day zero) on the day that the sponsor determines that a finding suggests a significant risk in humans. In general, it is not necessary for a final study report to be completed before a sponsor is able to make this determination.

H. Submission of Written Reports—Proposed § 312.32(c)(1)(iii)

Under proposed § 312.32(c)(1)(iii), FDA proposed that each written report may be submitted on an FDA Form 3500A or in a narrative format. Foreign SADRs may be submitted on an FDA Form 3500A or on a CIOMS I form. FDA also proposed that reports of overall findings or data in the aggregate from published and unpublished in vitro, animal, epidemiological, or clinical studies must be submitted in a narrative format. In addition, FDA proposed to require that each written notice bear prominent identification of its contents and be transmitted to the FDA review division that has responsibility for the review of the IND. FDA also proposed to require that if the agency determines that additional data are needed, FDA may require further data to be submitted.

The agency has also revised the requirement (final § 312.32(c)(1)(v)) to allow for electronic submission of these reports because the agency anticipates that these reports will be submitted by means other than paper in the future. In addition, the agency has revised the requirement to make clear that the period of time for submitting additional data requested by the agency is 15 calendar days, the same as required under § 312.32(d) for submitting followup information. The time for submission of this additional information was not specified in the proposed rule.

(Comment 30) Two comments asked if the agency would accept the CIOMS I form for reporting domestic SADRs. One comment strongly recommended that the CIOMS I form be acceptable for reporting domestic SADRs because it would decrease workload burden, enhance timeliness compliance with reporting timeframes, and integrate globally accepted formats.

(Response) FDA will continue, as proposed, the current practice of permitting submission of IND safety reports on FDA Form 3500A or in a narrative format for reports of domestic suspected adverse reactions and on FDA Form 3500A, in a narrative format or on a CIOMS I form for reports of foreign suspected adverse reactions. FDA declines to permit submission of domestic suspected adverse reactions on the CIOMS I form because the CIOMS I form has fewer data elements than FDA Form 3500A (see 60 FR 11284 at 11287, March 1, 1995; 62 FR 52237 at 52246, October 7, 1997) and FDA believes the additional data elements are useful for evaluating the report. FDA is continuing to accept the CIOMS I form for foreign reports because we believe that harmonization facilitates compliance with the reporting requirements, thereby expediting FDA's receipt of foreign suspected adverse reaction reports. In the future, the agency anticipates that electronic reporting of suspected adverse reactions will replace the use of paper forms.

I. Telephone and Facsimile Transmission Safety Reports—Proposed § 312.32(c)(2)

FDA proposed to require that the sponsor notify FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening SADR based on the opinion of the investigator or sponsor as soon as possible but in no case later than 7 calendar days after receipt by the sponsor of the minimum data set.

Because the agency anticipates that these reports will be submitted by means other than telephone or facsimile in the future (e.g., electronically), the agency has revised the requirement to eliminate the specificity that these reports be submitted only by telephone or facsimile. The agency also changed the paragraph heading to "Unexpected fatal or life-threatening suspected adverse reaction reports." For consistency with the agency's decision that assessment of whether the event is serious and unexpected should be based on the opinion of the sponsor (not the investigator), the agency eliminated the phrase "based on the opinion of the investigator or sponsor" (see comment 15 of this document and § 312.32(c)(1)(i)). For consistency with the agency's decision to eliminate the definition of "minimum data set," the agency replaced the phrase "after receipt by the sponsor of the minimum data set" in the proposed codified with "after the sponsor's initial receipt of the information" (see section III.C of this document).

J. Investigations of Marketed Drugs—Proposed § 312.32(c)(4)

FDA proposed that "a sponsor of a clinical study under an IND for a drug marketed in the United States is only required to submit IND safety reports to FDA (review division that has responsibility for the IND) for SADRs from the clinical study itself, whether from domestic or foreign study sites of the IND." As proposed, the sponsor would also be required to submit to FDA safety information from these clinical studies as prescribed by the postmarketing safety reporting requirements under §§ 310.305, 314.80, and 600.80.

(Comment 31) One comment supported the clarification of this requirement. Other comments requested further clarification. One comment asked what should be submitted to the IND from foreign studies not conducted under an IND (e.g., Phase 1–3 studies, Phase 4 postmarketing studies), both before and after a U.S. NDA is approved. One comment recommended that FDA finalize a provision to require that serious, unexpected SADRs that occur in studies not being conducted under an IND be submitted as expedited reports to an IND, if one exists. This comment also requested that FDA clarify whether serious, unexpected SADRs observed in IND-exempt studies of marketed drugs are required to be submitted to both an IND if one exists and the NDA. The comment recommended submitting these cases only to the NDA. One comment stated that although the requirement references the postmarketing safety reporting requirements, the postmarketing requirements do not mention foreign studies. This comment requested that FDA clarify the postmarketing requirements. Another comment stated that for products marketed and being studied globally, it is confusing to decide on the appropriate route of reporting given the different licensed status of products in different countries and different indications being investigated. This comment recommended that FDA provide a centralized reporting location so that FDA could route and file the report to the appropriate application.

(Response) The only reports that must be submitted to an IND for a drug marketed or approved in the United States are those arising from a study conducted under the IND (at domestic or foreign sites). All other reports (e.g., marketing experience, studies not under an IND), must be reported in accordance with the relevant postmarketing safety reporting requirements. In response to

the comments, the agency clarified § 312.32(c)(4) to state that a sponsor of a clinical study of a drug marketed or approved in the United States that is conducted under an IND is required to submit IND safety reports for suspected adverse reactions that are observed in the clinical study at domestic or foreign study sites. The sponsor must also submit safety information from the clinical study as prescribed by the postmarketing safety reporting requirements (e.g., §§ 310.305, 314.80, and 600.80).

Table 2 of this document summarizes the reporting requirements for the various scenarios identified in the comments about submitting safety reports from a clinical study.

TABLE 2.—SAFETY REPORTING REQUIREMENTS FROM CLINICAL STUDIES[1]

Drug marketed or approved[2] in the United States?	Under U.S. IND?	Trial site	Must report to IND?	Must report per post-marketing requirements?
Yes	Yes	U.S. or Foreign	Yes	Yes
Yes	No	U.S. or Foreign	No	Yes
No	Yes	U.S.or Foreign	Yes	
No	No	Foreign		

[1] Areas in the table are left blank when an IND or marketing application would not exist.
[2] If a drug is approved in the United States, but is not currently being marketed in the United States, the postmarketing requirements would still apply.

The agency does not agree with the comment that stated that the postmarketing requirements do not mention foreign studies. The postmarketing reporting requirements do apply to postmarketing studies conducted at foreign sites if the drug is marketed in the United States. For example, §§ 314.80(b) and 600.80(b) require applicants to review all adverse drug experience information from any source, "foreign or domestic," and §§ 314.80(e) and 600.80(b) require expedited reporting from a postmarketing study, whether or not conducted under an IND, if there is a reasonable possibility that the drug caused the adverse experience.

In addition, the agency revised the proposed language listing the postmarketing safety reporting requirements by including the parenthetical "(e.g., §§ 310.305, 314.80, and 600.80)," thereby clarifying that the listed postmarketing regulations are examples and other postmarketing safety reporting requirements may apply (e.g., reports related to certain over-the-counter (OTC) products under the Dietary Supplement and Nonprescription Drug Consumer Protection Act (Public Law 109–462); records regarding blood or blood products under § 606.170).

With respect to submitting reports to FDA to one central location, currently, postmarketing safety reports are entered into the Adverse Event Reporting System (AERS) database, whereas IND safety reports are sent directly to the review division that has responsibility for the review of the IND. Current capabilities do not permit direct electronic submission through a Web-based system. However, FDA is committed to adapting its business practices to evolving technology, including using the significant advancements in Web-based, electronic systems. We anticipate that, in future rulemakings, Web-based filing of most submissions will eventually be required. We anticipate that when such a change to an electronic submission system is implemented, future guidance will address any technical questions related to such submissions. Until such time that FDA develops a system to route and manage IND safety reports within the AERS database, or another database, the sponsor must submit them in the manner described in the regulations and to the appropriate FDA location identified in the regulations.

K. Followup—Proposed § 312.32(d)

Section 312.32(d) provides the requirements for investigating and submitting followup information to an IND safety report, making minor revisions in § 312.32(d)(2) to clarify how relevant followup information submitted under this paragraph must be identified (i.e., "Followup IND Safety Report"). The agency proposed revising the terminology in § 312.32(d)(3) to be consistent with the proposed use of the term SADR. The terminology in § 312.32(d)(3) is consistent with terms used in the final rule. Former § 312.32(d)(4) required that results of a sponsor's investigation of other safety information must be submitted, as appropriate, in an information amendment or annual report. The agency has eliminated this requirement because it is redundant—§§ 312.31 and 312.33 contain the submission requirements for information amendments and annual reports.

L. Disclaimer—Proposed § 312.32(e)

The agency proposed revising the terminology in § 312.32(e) to be consistent with the proposed use of the term SADR. The terminology in § 312.32(e) is consistent with terms used in the final rule.

M. Annual Reports

Although the agency did not propose any changes to the IND annual reporting requirements, FDA stated in the preamble to the proposed rule that it would not require reports of an increase in the rate of occurrence of expected, serious SADRs to be submitted to the agency in an expedited manner. The agency stated that instead, sponsors should report this information to FDA in their IND annual reports under § 312.33(b)(1) (68 FR at 12406 at 12425).

(Comment 32) One comment disagreed with FDA's proposal to deviate from the ICH E2A guidance, which recommends rapid communication to regulatory authorities for an increase in the rate of occurrence of an "expected," serious ADR that is judged to be clinically important (60 FR 11284 at 11286), because expedited reporting of this information may alert FDA to situations of more widespread and serious risks than were previously known or of use in populations that had not been previously identified as at risk. One comment agreed with the agency's departure from the ICH E2A guidance recommendation for expedited reporting of increased frequency of serious, expected SADRs. However, it questioned the utility of including this information in the IND annual report, as proposed by FDA. The comment stated that including this information may be difficult, given the timing of various

clinical trials relative to the IND annual reporting cycle. The comment suggested that rather than requiring increased frequency analysis of serious SADRs in IND annual reports, sponsors should routinely review incidence rates of all serious and nonserious adverse events within their clinical program, and report any significant changes in the IND annual report, when detected. Another comment recommended that the agency provide guidance on what would be deemed a "clinically important" increased rate of reports. The comment asked that FDA explain what the value added of such reporting is, given the agency's statements that such reports have limited reliability and have proven to be of little value in identifying increased incidences of serious, labeled events in the postmarketing setting (see 62 FR 34166, June 25, 1997).

(Response) To be consistent with the recommendations in the ICH E2A guidance and in response to comments about reporting serious)"expected" SADRs, the agency is adding a requirement under § 312.32(c)(1)(iv) that the sponsor expeditiously report any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. The agency acknowledges that baseline incidence rates from clinical trial data as a basis for comparison may not be available in all cases, and as explained in the preamble to the proposed rule (68 FR 12406 at 12425), for this reason, FDA did not explicitly propose to require these reports in the proposed rule. However, the agency believes that when rates are available, a clinically important increase provides important safety information and warrants expedited, rather than annual, reporting. Deciding if an increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure is) "clinically important" is a matter of judgment based on a variety of factors including the study population, the nature and seriousness of the reaction, and the magnitude of the observed increase in rate.

The agency also agrees with the comment that sponsors should routinely review incidence rates of all serious and nonserious adverse events within their clinical program and expects that this is current practice within the industry. If a clinically important increase in a serious suspected adverse reaction is identified when compared to the rate described in the protocol or investigator brochure, the sponsor must report it to FDA expeditiously. Changes in incidence rates for the most frequent nonserious adverse events would be reported in the IND annual report.

In response to the comment that requested clarification on the utility of these reports in the premarket setting when they have proven to be of little value in the postmarketing setting, the agency believes that there are differences between the premarket setting (where these reports would usually be based on incidence rates from clinical trials) and the postmarketing setting (where estimation of incidence rates from spontaneous reports is more difficult because, for example, the size of the exposed population is unknown). The agency believes that these reports contribute information important for understanding and updating the safety profile of the investigational drug product.

(Comment 33) Another comment noted that although FDA's proposed rule did not address the U.S. IND annual reporting requirements, it recommended that they be modified to be consistent with the ICH and EU annual reports in light of the finalization of the EU Clinical Trial Directive 2001/20/EC and the publication of their final detailed guidance.

(Response) The agency has been participating in the development of the ICH draft guidance, entitled "E2F Developmental Safety Update Report" (DSUR draft guidance), that describes the format, content, and timing for periodic reporting for an investigational drug. As stated in the notice announcing the availability of the DSUR draft guidance, the DSUR would serve as an internationally harmonized, annual clinical trial safety report that could be submitted in the United States in place of an annual report for an IND (73 FR 45462, August 5, 2008). After the DSUR draft guidance is finalized, the agency will evaluate the need to revise our IND annual reporting requirements to take into account international standards and recommendations.

(Comment 34) One comment requested clarification of IND annual reporting after an NDA has been approved and clinical studies continue under the IND, particularly in light of adoption of the PSUR, which includes clinical study data. The comment asked if safety sections in the IND annual report would be required after the NDA has been approved and the PSUR format is then being followed. The comment also requested clarification on whether the data cutoff date would be the IND effective date, the NDA approval date, or the international birth date.

(Response) Clinical development of a drug frequently continues even after it has been approved for marketing (e.g., for new indications, new dosage strengths, different populations). Therefore, the IND annual report continues to be important for evaluating and monitoring the safety of the drug. In addition, the DSUR draft guidance discusses the relationship between the DSUR and PSUR when clinical studies continue after a drug is approved for marketing, and when to initiate a DSUR for a marketed product. The guidance recommends that once a drug has received marketing approval in any country or region, and clinical trials continue or are initiated, both a PSUR and a DSUR should be prepared in accordance with directions from local authorities (DSUR draft guidance at p. 7). After the DSUR draft guidance is finalized, the agency will consider whether to revise our IND annual reporting requirements to take into account its current thinking on the issue, including adopting an international birthdate. Until that time, the data cutoff date for the IND annual report is the IND effective date because the annual report must be submitted to FDA within 60 days of the anniversary of the date that the IND went into effect (see § 312.33).

N. Investigator Reports—Proposed § 312.64(b)

FDA proposed to require that an investigator report to the sponsor any serious SADR immediately and any other SADR promptly unless the protocol or investigator's brochure specifies a different timetable for reporting the SADR.

(Comment 35) One comment suggested that FDA require investigators to report all protocol-defined treatment-emergent adverse events (TEAEs) expeditiously regardless of their causal attribution, but record their causality assessment when reporting such events. The comment defined a TEAE as an event that emerges during treatment having been absent pretreatment, or worsens relative to the pretreatment state. The comment stated that if the agency's SADR definition is implemented as proposed, it is conceivable that investigators will not report certain TEAEs if they feel a causal relationship can be ruled out. Because there are no standard guidelines for ruling out a possible causal relationship, there could be inconsistent causality assessments and adverse event reporting across study sites. Another comment stated that applying the SADR definition to investigator reporting could result in

underreporting of serious adverse events. The comment maintained that the investigator should report all serious adverse events to the sponsor, without making a causality assessment. The comment further stated that the proposed approach would not be in harmony with ICH standards and European regulatory requirements, which require that all serious adverse events be immediately reported to the sponsor. One comment stated that investigators provide an important and informed medical review of causality, especially in the presence of complex disease states where many adverse events occur as a result of the underlying disease process. The comment suggested that FDA provide clear guidance on reportable causality.

(Response) As noted in Comment 1 of this document, the agency has decided not to adopt the proposed SADR definition. FDA believes that there is more uncertainty when assessment of causality is based on an individual event rather than on aggregate data. The agency also believes that the sponsor is better positioned than the individual investigator to assess the overall safety of the investigational drug because the sponsor has access to serious adverse event reports from multiple study sites and is able to aggregate and analyze these reports. Therefore, the agency has determined that the sponsors should immediately receive reports from investigators of any serious adverse events, without regard to causality.

However, the agency agrees that, because the investigator is knowledgeable about the human subject (e.g., medical history, concomitant medications), administers the investigational drug, and monitors the subject's response to the drug, the investigator's view on the causal relationship between an adverse event and the investigational drug is important, especially in the presence of complex disease states where many adverse events occur as a result of the underlying disease process. Because the insight from the investigator is important for the sponsor to consider in assessing the safety of the drug and determining whether to report expeditiously to FDA, the agency has revised the requirement to require that the investigator include an assessment of causality in the report to the sponsor. Revised § 312.64(b) requires investigators to immediately report to the sponsor any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and the report must include an assessment of whether there is a reasonable possibility that the drug caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor.

(Comment 36) Several comments requested clarification of the terms "immediately" and "promptly" in the proposed requirement. The comments disagreed with the requirement to report other SADRs (i.e., nonserious) promptly to the sponsor, as the term "promptly" implies "quickly." The comments stated that nonserious SADRs are traditionally recorded on case report forms during the study, then verified and collected by the sponsor during scheduled monitoring visits. One comment recommended that the requirement be revised to require investigators to record, rather than report, other SADRs promptly.

(Response) The agency expects that, for serious adverse events, the investigator would notify the sponsor immediately. The agency recognizes that it may take a day to collect adequate information to confirm the occurrence of the adverse event but expects that as soon as the investigator has confirmed that the event occurred, the investigator will report it to the sponsor without delay.

The agency agrees with the comments that the term "promptly" does not appropriately describe the best process for documenting and notifying the sponsor about nonserious adverse events. Therefore, the agency has revised § 312.64(b) to state that the investigator must record nonserious adverse events and report them to the sponsor according to the timetable for reporting specified in the protocol. The sponsor would need to determine the appropriate interval for collecting and analyzing nonserious adverse event information based on the drug under investigation and other study considerations, and delineate the timetable in the protocol.

O. Bioavailability and Bioequivalence Requirements—Proposed § 320.31(d)

FDA proposed to require that persons conducting human bioavailability or bioequivalence studies that are not subject to an IND submit expedited safety reports to FDA in accordance with § 312.32. In the preamble to the proposed rule (68 FR 12406 at 12415), the agency stated that, in general, bioavailability and bioequivalence studies that are not being conducted under an IND are safe. However, the agency is occasionally made aware of safety-related information associated with these types of studies, which could reflect either a problem with the drug product being evaluated or with the study design being used. Timely review of this safety information is critical to ensuring the safety of study subjects. FDA proposed to require that these safety reports be transmitted to all participating investigators and to the appropriate FDA division in CDER (i.e., safety reports for the reference listed drug would be sent to the new drug review division that has responsibility for that drug, safety reports for the investigational drug product would be sent to the Director, Division of Bioequivalence, Office of Generic Drugs) and each report bear prominent identification of its contents. For reporting purposes under § 320.31(d)(3), an unexpected SADR would be any SADR the specificity or severity of which is not consistent with the U.S. labeling for the reference listed drug.

In general, the occurrence of a serious adverse event is very unusual in a bioavailability or bioequivalence study because the number of subjects enrolled in the study is small, the subjects are usually healthy volunteers, and drug exposure is typically brief. For these reasons, the occurrence of any serious adverse event is of interest. The agency reviewed the numbers and types of serious adverse events that we have received from these trials (i.e., in study reports submitted in abbreviated new drug applications (ANDAs)), and determined that they are typically listed in the labeling of the reference listed drug and, therefore, would not be subject to reporting under § 312.32(c)(1)(i) as serious and unexpected suspected adverse reactions because they would not meet the regulatory definition of "unexpected." In addition, because serious adverse events are so unusual in these studies, FDA believes that the causality assessment is unnecessary under these circumstances and that it is important to review all serious "adverse events." Thus, the proposed requirement to report serious and unexpected SADRs would not have served its intended purpose of alerting the agency to serious adverse events occurring in these trials, so the agency has revised the requirement. The agency continues to believe that receiving reports from these trials is important for human subject protection and, therefore, has revised § 320.31(d)(3) to require that any serious adverse event must be reported, instead of any serious and unexpected SADR. The person

conducting the study, including any contract research organization, must notify FDA and all participating investigators of any serious adverse event, as defined in § 312.32(a), from the study as soon as possible but in no case later than 15 calendar days after becoming aware of its occurrence. Each report must be submitted on FDA Form 3500A or in an electronic format that FDA can process, review, and archive. FDA will periodically issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation, and organization of files). As proposed, each report must bear prominent identification of its contents, i.e., "bioavailability/bioequivalence safety report." The person conducting the study, including any contract research organization, must also notify FDA of any fatal or life-threatening adverse event from the study as soon as possible but in no case later than 7 calendar days after becoming aware of its occurrence. Each notification under § 320.31(d)(3) must be submitted to the Director, Office of Generic Drugs in CDER. Relevant followup information to a bioavailability/bioequivalence safety report must be submitted as soon as the information is available and must be identified as such, i.e., "Followup bioavailability/bioequivalence safety report." Upon request from FDA, the person conducting the study, including any contract research organization, must submit to FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 days after receiving the request.

(Comment 37) Some comments requested clarification about the requirement to submit expedited safety reports for qualifying SADRs that arise in human bioavailability and bioequivalence studies that do not require an IND. The comments requested that the agency clarify whether this includes studies conducted outside of the United States and how these reports should be submitted in the absence of an IND.

(Response) Under § 320.31(d)(3), sponsors of human bioequivalence or bioavailability studies that are exempt from the IND requirements under part 312, but are conducted in the United States, must report any serious adverse events from the study to FDA (to the Office of Generic Drugs in CDER) and to all participating investigators. These requirements do not apply to human bioavailability and bioequivalence studies that are exempt from the IND requirements under part 312 and are conducted outside of the United States. However, as part of the information required to establish that the proposed drug product can be expected to have the same therapeutic effect as the reference listed product, adverse event reports that occurred in foreign clinical studies must be included in the ANDA submission (see § 314.94(a)(7)).

P. Reports to Investigators and IRBs

In proposed § 312.32(c)(1)(i) and (c)(1)(ii), FDA proposed to require that sponsors notify FDA and all participating investigators in a written IND safety report of any serious and unexpected SADR or information sufficient to consider product administration changes. Although both of these requirements have been revised (see response to Comments 15 to 17 and 23 to 29 of this document), the requirement that FDA and all participating investigators receive IND safety reports for potential serious risks that emerge during the conduct of a clinical investigation has not changed in this final rule (see final § 312.32(c)(1)).

In addition, under current § 312.66, the investigator must, among other things, assure that he or she will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that he or she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects. The agency did not propose any changes to this requirement.

(Comment 38) Some comments pointed out that the proposed rule did not change the frequency or format for providing clinical investigators with information on serious, unexpected adverse events associated with the use of a drug. One comment agreed that it is imperative that investigators responsible for the conduct of studies be informed by the sponsor of findings that could adversely affect the safety of study participants. However, the comment noted that this process can be confusing and overwhelming, particularly for investigators of IND studies conducted outside the United States. Several comments proposed alternative reporting approaches that would provide investigators with reports that are more useful and efficient and less confusing. One comment recommended that the requirements for notifying all participating investigators be changed to allow a periodic summary and analysis of qualifying SADRs rather than individual reports that are difficult to track, aggregate, analyze, and interpret at the investigational site. Several comments encouraged FDA to further harmonize with CIOMS VI and the EU Clinical Trial Directive approach for investigator notification because: (1) Periodic (quarterly) aggregate line listings of suspected unexpected serious adverse reactions (SUSARs) accompanied by a summary of the evolving safety profile would provide useful information to investigators and IRBs, especially for Phase l–3 studies; (2) presenting all serious, unexpected, associated events in line listings regardless of medication administered (e.g., active drug, comparator, or placebo) would maintain the blind to the investigator; and (3) significant safety issues would be communicated as soon as possible to the investigators. These comments stated that investigators would recognize that these expedited communications represent significant safety information that is to be immediately reviewed and provided to their IRBs. The comments noted that expedited reporting to FDA and processes for updating the investigator brochure would remain unchanged.

In addition, one comment requested that FDA not require investigator notification letters for investigations of marketed products, even if conducted under an IND, unless the investigation is for a patient population or indication that is different from that approved. The comment stated that any significant new safety information will be evaluated by the sponsors as part of their signal detection process and, if necessary, will be incorporated in the product label. The comment recommended that FDA allow periodic line-listings to be sent to investigators in lieu of individual reports.

(Response) The agency is aware that for large, multi-center trials, investigators have expressed concern about receiving large numbers of individual adverse event reports that may not be useful. The agency believes that these final requirements will significantly diminish the numbers of individual reports that, in isolation, do not provide useful information to the investigator. For example, the requirement under § 312.32(c)(1)(i), described in the response to Comment 18 of the document, makes it clear that specific events (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) are to be reported to FDA and all participating investigators only if there is evidence, based on an aggregate analysis, to suggest a causal relationship between the drug product and the adverse event. The rule also makes it

clear that study endpoints would ordinarily not be reported as serious, unexpected suspected adverse reactions (response to Comment 19 of this document). These clarifications are expected to reduce the number of reports that do not contribute in a meaningful way to the developing profile of the drug.

FDA does not agree with the comment that suggested that investigators not be notified of serious, unexpected suspected adverse reactions from investigations of marketed products unless the investigation is for a patient population or indication different from that approved. Regardless of the patient population or indication, information about a serious, unexpected suspected adverse reaction may influence the investigator's management of a clinical trial participant and, is therefore, critical information for the investigator to receive.

(Comment 39) Some comments stated that although the IRB's charge is to have written procedures for reporting "any unanticipated problems involving risks to human subjects or others," the proposed rule is silent about sending any information to IRBs. These comments recommended that the agency provide guidance to sponsors, manufacturers, investigators, and IRBs that clearly delineates the responsibilities of reporting SADRs to the IRB. One comment requested that FDA require that the IRB receive from the sponsor the same expedited reports that the sponsor sends to FDA and all participating investigators (under proposed § 312.32(c)(1)). Other comments pointed out that IRBs are currently overwhelmed with IND safety reports and recommended that sponsors provide IRBs with routine timely aggregated reports of listings of adverse events instead of individual reports. Another comment suggested that investigators be permitted to provide these line-listings to their IRBs in lieu of individual reports. One comment urged FDA to adopt the CIOMS VI recommendations for IRB notification.

(Response) The agency concurs with the overall sentiments expressed by the comments and has provided recommendations for reporting adverse event information to IRBs in our "Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting—Improving Human Subject Protection." We also expect that the more useful individual reports submitted by sponsors to FDA and investigators will translate into more useful information being provided by investigators to their IRBs. In addition, the agency may consider revisions to investigator reporting requirements to IRBs in a separate rulemaking initiative.

Q. Miscellaneous Comments

FDA stated in the preamble to the proposed rule that the term "sponsors" would be used to describe persons subject to the premarketing safety reporting regulations (68 FR 12406 at 12412).

(Comment 40) Two comments asked FDA to clarify how the safety reporting requirements apply to investigator-initiated studies, since such studies are not mentioned in the agency's definition of "sponsors."

(Response) The agency considers investigator-initiated studies to be synonymous with studies conducted by a sponsor-investigator. A sponsor-investigator, as defined in § 312.3, is "an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. The term does not include any person other than an individual. The requirements applicable to a sponsor-investigator under this part [312] include both those applicable to an investigator and a sponsor." Therefore, the safety reporting requirements under § 312.32 would apply to an investigator-initiated study.

(Comment 41) One comment suggested that FDA request that the National Institutes of Health (NIH) and other Federal agencies that have agreed to the Federal Policy for the Protection of Human Subjects (Common Rule) also adopt the proposed regulations. The comment stated that all participants in the research enterprise must be fully committed to the protection of research participants, and fostering better and more complete safety reporting will support that commitment.

(Response) This final rule would apply to FDA-regulated research conducted by NIH and other Federal agencies. The agency agrees that improved safety reporting should enhance the protection of human subjects participating in clinical trials.

(Comment 42) FDA proposed that the final rule would become effective 180 days after its date of publication in the **Federal Register**, except for any final rule regarding the proposal to require that postmarketing SADRs in the individual case safety reports be coded using the Medical Dictionary for Regulatory Activities (MedDRA), which would become effective 1 year after its date of publication in the **Federal Register**.

Many comments expressed concern that the proposed timeline for implementing the new requirements is too aggressive, given its impact on systems and processes (e.g., to develop, test, and validate a new system). Some comments did not believe 180 days was sufficient implementation time unless the final rule was significantly modified. One comment requested that FDA allow for a transition period for ongoing clinical trials if FDA continues with its interpretation of "related," as used in the proposed SADR definition. One comment agreed with the adoption of MedDRA for premarketing safety reporting for clinical trials, but did not believe that the 1-year proposed timeline was realistic. Comments requested other implementation schedules, ranging from 12 to 18 months for all the requirements.

(Response) The agency does not agree that an effective date of 180 days after the date of publication in the **Federal Register** is too aggressive. The agency believes that the revisions to the requirements in this final rule will streamline adverse event reporting and are crucial to ensuring that timely and accurate safety information about clinical trials is received, analyzed, and disseminated. Therefore, as proposed, the agency has retained the effective date for the final rule to be 180 days after the date of publication in the **Federal Register**. The concerns raised by the comments about the agency's interpretation of "related" are no longer an issue because the agency did not adopt the SADR definition. In addition, the agency did not propose, and is not requiring in this final rule, the use of MedDRA for IND safety reporting.

R. Initial Analysis of Impacts and Paperwork Burden Estimates

For the initial analysis of impacts, FDA estimated the costs of adding the new premarketing safety reporting requirements (68 FR 12406 at 12456 and 12457, table 14) (see section VI of this document for discussion). For the initial paperwork burden estimates, FDA estimated the total annual reporting burden associated with the premarketing safety reporting requirements, accounting for not only the additional burdens associated with the proposed new requirements, but also for burdens already approved by the Office of Management and Budget (OMB) for requirements under then-current §§ 312.32 and 312.64 (68 FR 12406 at 12470, table 21) (see section VII of this document for further discussion).

For narrative reports based on information sufficient to consider a change in product administration (discussed in section III.G of this document), for the initial analysis of

impacts, FDA estimated that sponsors would spend an additional 4 hours per report for up to 600 IND safety reports. For the paperwork burden, however, for the same 600 IND safety reports, FDA estimated that sponsors would spend a total of 8 hours per report. The 4-hour per report estimate in the initial analysis of impacts accounted only for the incremental burden of the proposed reports from in vitro studies, epidemiological studies, and clinical studies and did not account for required reports of "any finding from tests in laboratory animals that suggests a significant risk in human subjects" under then-current § 312.32(c)(1)(i)(B). However, the 8-hour per report paperwork burden estimate accounted not only for the burden of complying with the new proposed requirements, but also the then-current requirement to submit reports from animal tests.

(Comment 43) Comments from industry stated that FDA underestimated the number of IND safety reports and that the proposed SADR definition could increase the volume of IND safety reports from 2-fold to 10-fold. Furthermore, comments claimed that any additional reports would be uninformative. An increase in the number of uninformative safety reports would create an additional burden on investigators and IRBs without a corresponding benefit. Comments noted that FDA's analysis failed to account for the potential impact of these additional reports on IRBs and investigators. Moreover, in some cases, additional uninformative reports could force sponsors to unnecessarily break the blind of a clinical trial, potentially reducing the power of double-blind clinical trials to detect safety issues and imposing additional burdens to industry.

(Response) As discussed in response to Comment 1 of this document, the agency has decided not to adopt the proposed SADR definition, and instead adopted definitions for the terms "adverse event" and "suspected adverse reaction." In addition, FDA clarified the circumstances under which IND safety reports need to be submitted. With these changes, we expect fewer reports. Therefore, the comments stating that FDA underestimated the number of IND safety reports have been addressed.

(Comment 44) Some industry comments stated that FDA underestimated the number of hours required to prepare a narrative report based on information sufficient to consider changes in product administration or risk profile. These comments stated that preparing a narrative report requires more than 8 hours.

(Response) Although comments stated that preparing a narrative report requires more than 8 hours, none of these comments provided estimates for a specific number of hours. Without other information, we are unable to respond directly to these comments. Nevertheless, we recognize that there may be some situations and types of findings that would require sponsors to spend more time preparing a narrative report. Therefore, to capture the uncertainty of this estimate, FDA has decided to use a range of hours (from 4 to 12 hours) to estimate the incremental burden of this requirement instead of the 4-hour estimate used in our initial analysis of impacts (section VI of this document) or the total 8-hour estimate used in the initial paperwork burden analysis (section VII of this document).

IV. Legal Authority

The premarket approval provisions of the act authorize FDA to require that drug labeling provide the practitioner with adequate information to permit safe and effective use of the drug product. Section 505 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355) requires us to weigh evidence of effectiveness and safety to determine whether the evidence supports drug approval, whether data are adequate to permit a clinical investigation to proceed under the IND regulations, and/or whether a product is appropriately labeled. Section 351(a)(2)(C)(i)(1)) of the Public Health Service Act (the PHS Act) (42 U.S.C. 262(a)(2)(C)(i)(I)) authorizes the agency to approve a biologics license application (BLA) only if the applicant demonstrates that the product is safe, pure, and potent. Section 351(a)(2)(A) of the PHS Act authorizes the agency to establish, by regulation, requirements for the approval, suspension, and revocation of biologics licenses. Section 701(a) of the act (21 U.S.C. 371(a)) authorizes FDA to issue regulations for the efficient enforcement of the act. These statutory provisions authorize us to issue regulations requiring sponsors to submit safety information to the agency to support an IND, NDA, ANDA, or BLA.

V. Environmental Impact

The agency has determined under 21 CFR 25.30(h) 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.

VI. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 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). The agency believes that this final rule is not a significant regulatory action under the Executive order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the new reporting requirements are likely to impose a minimal burden on small entities (less than 0.2 percent of the average value of shipments of entities with less than 10 employees), the agency believes that the final rule will probably 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 that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "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 $135 million, using the most current (2009) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this final rule to result in any 1-year expenditure that would meet or exceed this amount.

In accordance with Executive Order 12866, FDA has previously analyzed the potential economic effects of the proposed rule. Although FDA determined that the proposed rule was an economically significant rule as described in the Executive order, the final rule covers a smaller subset of the proposed regulatory actions and is only related to premarket safety reporting and safety reporting for certain bioavailability and bioequivalence studies. Consequently, the annual estimated costs of this final rule are projected to equal less than $0.7 million. We are unable to quantify the benefits of the final rule, but expect that

the potential benefits of harmonized and improved safety reporting will justify the minimal costs of this rule.

A. Need for the Regulation

Ambiguous regulatory requirements may cause sponsors to unnecessarily submit certain IND safety reports to FDA and investigators. As described in section I of this document, lack of clarity about definitions and regulatory reporting requirements may create uncertainty about when to submit an IND safety report and may lead to over- or underreporting to FDA and investigators. Uncertainty about safety reporting requirements can result in reports being submitted for adverse events when there is little evidence of a causal relationship between the drug and the adverse event. Such reports can produce so-called "noise" in the system and hinder the development of the premarket safety profile of an investigational drug. Conversely, exempting certain bioavailability and bioequivalence studies from safety reporting requirements may lead to underreporting of some serious adverse events.

The rule will finalize definitions and IND safety reporting standards that are as consistent as possible with ICH documents, require expedited reporting of study findings suggesting a significant risk to humans, and establish reporting requirements for certain bioavailability and bioequivalence studies. Moreover, the final rule clarifies when certain safety information, such as study endpoints, should be reported, potentially reducing the number of uninformative reports sent to FDA, participating investigators, and IRBs.

B. Costs of the Regulation (to Prepare and Submit Safety Reports)

1. Number of Reports

For the initial analysis of impacts, we estimated that sponsors would submit up to 200 reports per year to comply with the new requirement for safety reporting of bioavailability and bioequivalence studies under proposed § 320.31(d). No comments were received on this estimate. Consequently, in the final analysis of impacts, we retain our original estimate of 200 reports per year.

In the initial analysis of impacts, we estimated that sponsors would submit up to 600 written IND safety reports annually based on information sufficient to consider a change in product administration (proposed § 312.32(c)(1)(ii))[3]. Consistent with ICH recommendations for IND safety reporting, the proposed rule would have clarified that sponsors should submit written IND safety reports when they receive information suggesting significant human risk sufficient to consider changes in the conduct of a clinical trial or product administration. Information suggesting a significant human risk could come from animal studies, in vitro studies, epidemiological studies, or clinical studies. We received no comments on this estimate.

In contrast to the ICH recommendation that sponsors rapidly report an increase in the rate of occurrence of an expected, serious SADR, the preamble of the proposed rule noted that sponsors should submit this type of information in IND annual reports under § 312.33(b)(1) (68 FR at 12406 at 12425). Because no changes to the IND annual reports were proposed, FDA did not estimate the incremental impact of these reports. For the final rule, however, increases in the occurrence rates of serious suspected adverse reactions over that listed in the protocol or investigator brochure must be reported as expedited IND safety reports. We have insufficient information to determine the potential impact of reporting increases in occurrence rates of serious suspected adverse reactions over that listed in the protocol or investigator brochure as expedited reports as opposed to including this information in annual reports. As part of good clinical practice, sponsors routinely review and analyze the incidence rates of serious and nonserious adverse events of their investigational drugs. Therefore, we expect that the incremental burden of this requirement will be minimal and estimate that sponsors will submit up to 10 additional reports per year.

Furthermore, the final rule clarifies the definition of a suspected adverse reaction for reporting purposes (§ 312.32(a)) and adds a requirement that sponsors only submit reports of study endpoints in unusual circumstances not described in the protocol (§ 312.32(c)(5)). We anticipate that by clarifying what is a suspected adverse reaction for reporting purposes and the circumstances under which study endpoints should be submitted as expedited reports, the number of uninformative expedited reports will be reduced, thus reducing the burden on sponsors, investigators, IRBs, and FDA. However, we have no information to estimate the magnitude of this reduced burden.

Last, the final rule clarifies safety reporting requirements for investigators to report to sponsors (§ 312.64(b)). Instead of requiring that investigators promptly report any adverse event reasonably caused or probably caused by the drug, the final rule requires that investigators immediately report any serious adverse event to the sponsor and include an assessment of whether there is a reasonable possibility that the drug caused the event. Because it is common practice for sponsors to outline similar reporting responsibilities in their clinical trial protocols, we assume that this final requirement will impose no additional burden.

2. Costs to Prepare and Submit Safety Reports

As shown in table 3 of this document, we estimate that it takes an average of 14 hours to prepare a safety report for a bioavailability and bioequivalence study. Based on 2007 hourly median wages for the pharmaceutical manufacturing industry, each of these reports will cost sponsors about $950.

As discussed in Comment 44 of this document, the additional time needed to prepare a report of findings suggesting a significant risk in humans may vary. We estimate that sponsors could spend from 4 to 12 hours additional time to prepare a narrative IND safety report. The average incremental cost of a narrative IND safety report ranges from $250 to $750 (table 3 of this document).

[3] The proposed premarketing reporting requirement revised the existing requirements and expanded the types of findings that sponsors should report as expedited narrative IND safety reports. As discussed in sections III.R and VII of this document, the estimated average incremental burden of the regulatory action in the initial analysis of impacts (i.e., 4 hours) accounted for then-current compliance (i.e., reports based on findings from animal tests) under then-current § 312.32(c)(1)(i)(B)).

TABLE 3.—ESTIMATED INCREMENTAL BURDEN AND UNIT COSTS FOR IND SAFETY REPORTS

Type of Report	Burden (hours) and Type of Expertise Required			Total Burden (hours)	Total Cost ($)[4]
	Clerical[1]	Epidemiology and Clinical Medicine[2]	Regulatory Affairs[3]		
Bioavailability and Bioequivalence Safety Reports	2	1	11	14	950
IND Safety Reports—lower estimate[5]	1	1	2	4	250
IND Safety Reports—upper estimate[5]	3	3	6	12	750

Numbers are rounded.
Source: U.S. Department of Labor, Bureau of Labor Statistics, May 2007 (Ref. 4).
[1] Based on median hourly wages for Office and Administrative Support Occupations (43–0000) and 40 percent benefits ($24.43 = $17.44 x 1.4).
[2] Based on median hourly wages for Medical and Health Services Managers (11–9111) and 40 percent benefits ($75.03 = $53.59 x 1.4).
[2] Based on median hourly wages for Medical and Health Services Managers (11–9111) and 40 percent benefits ($75.03 = $53.59 x 1.4).
[3] Based on median hourly wages for Management Occupations (11–0000) and 40 percent benefits ($74.96 = $53.54 x 1.4).
[4] Unit costs are rounded.
[5] Includes reports based on findings suggesting a significant risk in humans from epidemiological studies, pooled analysis of multiple studies, other clinical studies, or in vitro testing. Reports from animal testing are not included (see footnote 3 of this document).

Table 4 of this document summarizes the estimated total costs of the final rule. Annually, sponsors will submit up to 200 safety reports for bioavailability and bioequivalence studies and up to 610 IND safety reports. We estimate that the total costs of the final rule will equal less than $0.7 million annually.

TABLE 4.—ESTIMATED TOTAL COSTS OF THE FINAL RULE

Type of Report	Unit Costs ($)	Annual No. of Reports	Total Annual Costs ($)
Bioavailability and Bioequivalence Safety Reports[1]	950	200	190,000
IND Safety Reports[2]	250 to 750	610	150,000 to 460,000
Total Costs			340,000 to 650,000

Numbers are rounded; total costs are rounded to the nearest ten thousand dollar increment.
[1] We received no comments that provided sufficient information to revise our initial estimate. Because these events occur sporadically and the number of reports will vary from year to year, these numbers represent reasonable estimates of the annual average number of reports.
[2] The annual number of IND safety reports includes the proposed 600 reports of information suggesting a significant human risk (from epidemiological studies, pooled analysis of multiple studies, other clinical studies, or in vitro testing, but not from animal testing (see footnote 3 of this document)) and an additional 10 reports of increases in the occurrence rates of serious suspected adverse reactions over that listed in the protocol or investigator brochure.

C. Benefits of the Regulation

Benefits for the initial analysis of impacts were based on potential improvements in public health from better postmarket safety reporting and surveillance. The definitions and other requirements of the final rule provide a standardized framework against which adverse events and adverse reactions can be evaluated, reducing ambiguity and uncertainty about when and how to submit IND safety reports.

The final rule adds a requirement to submit safety reports for certain bioavailability and bioequivalence studies that have been exempt from safety reporting. These studies have been exempted from safety reporting requirements because serious adverse events in these types of studies are rare. As described elsewhere in this document, most serious adverse events would be listed in the labeling of the reference listed drug and thus would not meet the threshold for expedited IND safety reporting. However, reporting such unusual events would alert FDA to serious adverse events occurring in these trials. For this reason, it is prudent that FDA review such safety information. However, we lack sufficient information to estimate the magnitude of these potential benefits.

The revised IND safety reporting requirements will clarify when a sponsor should send a narrative IND safety report to FDA and participating investigators. Regardless of who conducts a study or whether a study is conducted under an IND, any finding that suggests a significant risk to humans must be reported as an expedited report. A risk is considered significant if it will ordinarily result in a safety-related change in the protocol, informed consent, investigator brochure, or conduct of the clinical investigation. Findings of a significant risk to humans can come from many sources, including epidemiological studies, pooled analysis of multiple studies, clinical studies, animal testing, or in vitro testing. Expedited reports of important safety information will enable FDA to more quickly review and monitor the safety profile of investigational drugs. However, because we lack estimates of the impact of expedited reporting on drug safety, we are not able to estimate the potential benefits of this reporting requirement.

The final rule includes a new requirement to report clinically important increases in the occurrence rates of serious suspected adverse reactions over that listed in the protocol or investigator brochure as expedited IND safety reports. Because these reports are usually based on incidence rates from clinical trials (i.e., known exposure rates), such reports can alert FDA to previously undetected human safety risks. Although these reports can occur sporadically, such reports can provide important information that

could affect drug safety profiles. However, we lack sufficient information to estimate the magnitude of these potential benefits.

Uncertainty about reporting requirements can lead sponsors to overreport or underreport safety events. Overreporting can introduce so-called "noise" that can delay the detection of possible safety problems. Underreporting potential safety problems can also delay identification of an important new risk. We expect that the final rule will remove some of the uncertainty that may lead sponsors to over- and underreport adverse events. In addition, we expect that FDA will receive expedited reports of safety information that suggest a significant risk in humans. Such reports can promote timely review of important drug safety information. Although we are unable to make a quantitative estimate of the benefits of the final rule, we believe that the potential benefits realized through more informative, accurate, and timely safety reports will justify the minimal costs of the final rule.

D. Final Regulatory Flexibility Analysis

This final rule will harmonize certain FDA safety reporting requirements with international initiatives and improve the quality of safety reporting for IND products and certain marketed products. According to the Table of Small Business Size Standards, the U.S. Small Business Administration (SBA) considers pharmaceutical preparation manufacturing entities (NAICS 325412) with 750 or fewer employees and biological product manufacturing entities (NAICS 325414) with 500 or fewer employees to be small. Statistics on the classification of firms by employment size from the U.S. Bureau of the Census show that in 2005, at least 85 percent of pharmaceutical manufacturing and biological product manufacturing entities had fewer than 500 employees and would have been considered small by SBA.

Entities have sufficient expertise to comply with the new safety reporting requirements. As shown in table 5 of this document, the unit costs of a safety report total less than 0.2 percent of the average value of shipments for the smallest entities. As further explained previously, the agency does not believe that this final rule will have a significant economic impact on a substantial number of small entities, but the impact is uncertain. Although some final requirements extend to investigators, we anticipate no additional burden on investigators who would meet the SBA definition of small entity.

TABLE 5.—UNIT COSTS OF SAFETY REPORTS AS A PERCENTAGE OF THE AVERAGE VALUE OF SHIPMENTS FOR VERY SMALL ESTABLISHMENTS

	Pharmaceutical Preparation Manufacturing (NAICS 325412)[1]		Biological Product Manufacturing (NAICS 325414)[2]	
No. of employees	<5	<10	<5	<10
Total value of shipments ($1,000)	187,933	561,636	32,011	115,307
No. of establishments	228	339	67	109
Average value of shipments ($)	824,268	1,656,743	477,776	1,057,862
Unit costs of an IND safety report as a percentage of the average value of shipments[3]	0.0% to 0.1%	0.0% to 0.0%	0.1% to 0.2%	0.0% to 0.1%
Unit costs of a bioavailability or bioequivalence report as a percentage of the average value of shipments[4]	0.1%	0.1%	0.2%	0.1%

Numbers are rounded.
[1] Source: U.S. Department of Commerce, Bureau of the Census, 2002 (Ref. 5).
[2] Source: U.S. Department of Commerce, Bureau of the Census, 2002 (Ref. 6).
[3] Based on a unit cost ranging from $250 to $750.
[4] Based on a unit cost = $950.

VII. Paperwork Reduction Act of 1995

This final rule contains information collection requirements that are subject to review by OMB under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520) (the PRA). The title, description, and respondent description of the information collection provisions are shown in the following paragraphs with an estimate of the annual reporting burden. Our estimate includes the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information, not accounted for under then-current § 312.32 or § 312.64, already approved by OMB (OMB control number 0910–0014).

Title: Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans

Description: The final rule clarifies the agency's expectations for timely review, evaluation, and submission of relevant and useful safety information and implements internationally harmonized definitions and reporting standards for IND safety reports. The final rule also subjects bioavailability and bioequivalence studies to safety reporting requirements. The final rule is intended to improve the utility of IND safety reports, expedite FDA's review of critical safety information, better protect human subjects enrolled in clinical trials, and harmonize safety reporting requirements internationally.

The Final Rule and Estimates of Reporting Burden

The rule finalizes revisions to the IND safety reporting requirements found in part 312 and the safety reporting requirements for bioavailability and bioequivalence studies found in part 320. For the initial PRA analysis for the proposed rule, FDA estimated for the annual reporting burdens for collections of information for the entire proposal (i.e., pre- and postmarketing safety reporting requirements). For this PRA analysis, FDA has estimated only for the annual reporting burdens for collections of information included in this final rule (i.e., requirements found in

§§ 312.32, 312.64, and 320.31). In addition, in the initial PRA analysis for the proposed rule, FDA estimated for the total reporting burden associated with the proposed reporting requirements in §§ 312.32, 312.64, and 320.31 (as opposed to only the increased burdens associated with the proposed rule). Because OMB has approved paperwork burdens for many of the reporting requirements found in §§ 312.32 and 312.64, for purposes of this final rule and this PRA analysis, FDA is providing estimates for only the additional burdens not already approved by OMB for §§ 312.32, 312.64, and 320.31 (OMB control number 0910–0014). The following provisions of the final rule contain collections of information and the following burden estimates are based on those discussed in the Analysis of Impacts (section VI.B of this document).

Section 312.32(c)(1)(i) specifies the requirements for reporting to FDA in an IND safety report potential serious risks from clinical trials within 15 calendar days for reports of serious and unexpected suspected adverse reactions and provides examples of what evidence supports a suggestion that there is a causal relationship between the drug and the adverse event. For purposes of this final rule, there is no new information collection because the reporting burden is unchanged from former § 312.32 and the information collection is already approved by OMB (OMB control number 0910–0014).

Section 312.32(c)(1)(ii) requires reporting to FDA in an IND safety report potential serious risks from clinical trials within 15 calendar days for findings from epidemiological studies, pooled analyses of multiple studies, or other clinical studies that suggest a significant risk in humans exposed to the drug. This reporting requirement was not included in former § 312.32. Section 312.32(c)(1)(iii) specifies the requirements for reporting to FDA in an IND safety report potential serious risks from clinical trials within 15 calendar days for findings from animal or in vitro testing that suggest a significant risk to humans. While reports from in vitro testing that suggest a significant risk to humans were not required to be reported under former § 312.32, reports from any finding from tests in laboratory animals were required to be reported (former § 312.32(c)(1)(i)(B)). For purposes of this final rule, for the provisions that are unchanged from former § 312.32, the information collection is already approved by OMB (OMB control number 0910–0014). For the additional reporting requirements (i.e., the proposed narrative reports excluding animal testing) in the initial PRA analysis, FDA estimated that sponsors would spend a total of 8 hours per report to prepare and submit these narrative reports. In response to comments, FDA has revised the estimate from an incremental 4 hours to a range from 4 hours to 12 hours per report. Given this range, the upper estimate of additional paperwork burden associated with this requirement for each applicant could be an additional 12 hours to prepare each narrative report. Therefore, for an additional 600 reports, FDA estimates the total annual reporting burden of this final rule could be as high as 7,200 hours.

Section 312.32(c)(1)(iv) requires reporting to FDA in an IND safety report within 15 calendar days any clinically important increase in the rate of occurrence of serious suspected adverse reactions over that listed in the protocol or investigator brochure (§ 312.32(c)(1)(iv)). These reports were not required to be submitted within 15 days under former § 312.32. FDA estimates that the minimal incremental burden for this requirement to be approximately 10 reports per year. Using the same upper estimate for the burden as discussed previously (i.e., 12 hours to prepare each report), FDA estimates the additional burden associated with this requirement could be as high as 120 hours. We request industry to comment on whether the requirement will impose an increased burden and if so, provide an estimate of the reporting burden.

Section 312.32(c)(2) requires reporting within 7 days any unexpected fatal or life-threatening suspected adverse reaction. For purposes of this final rule, there is no new information collection because the reporting burden is unchanged from former § 312.32 and the information collection is already approved by OMB (OMB control number 0910–0014).

Section 312.32(c)(4) requires a sponsor of a clinical study of a drug marketed or approved in the United States that is conducted under an IND to submit safety reports for suspected adverse reactions that are observed in the clinical study. For purposes of this final rule, there is no new information collection because the reporting burden is unchanged from former § 312.32 and the information collection is already approved by OMB (OMB control number 0910–0014).

Section 312.32(c)(5) clarifies the circumstances under which study endpoints should be submitted to FDA. FDA believes that these clarifications to former § 312.32 are likely to result in a reduction in the number of expedited reports that currently are accounted for by OMB. However, FDA has insufficient information to provide an estimate and was unable to ascertain from industry an estimate for such a reduction. Therefore, FDA requests that industry comment on the impact of this provision on reporting burdens. Any reduction in reports will be reflected the next time the information collection for § 312.32 (OMB control number 0910–0014) is extended.

Section 312.32(d)(1)-(3) requires followup reporting requirements. For purposes of this final rule, there is no new information collection because the reporting burden is unchanged from former § 312.32 and the information collection is already approved by OMB (OMB control number 0910–0014).

Section 312.64(b) requires investigators to report immediately to the sponsor any serious adverse event and include an assessment of whether there is a reasonable possibility that the drug caused the event. FDA revised former § 312.64(b) for clarity and to reflect current practices for investigator reporting to sponsors. For purposes of this final rule, there is no new information collection because we believe that the reporting burden is unchanged from former § 312.64 and the information collection is already approved by OMB (OMB control number 0910–0014).

Finally, § 320.31(d)(3) subjects bioavailability and bioequivalence studies to safety reporting requirements. This reporting requirement was not included in former § 320.31. Therefore, all of these reports would be new. For purposes of the initial PRA analysis and this PRA analysis, FDA estimated up to 200 new safety reports required under § 320.31(d) from bioavailability and bioequivalence studies. For these 200 reports, FDA estimates that it could take applicants an additional 14 hours to prepare and submit each report. The burden for bioavailability and bioequivalence safety reporting requirements would total 2,800 hours per year as a result of this final rule.

Description of Respondents: Business or other for-profit organizations.

Table 6 of this document presents the estimated annualized reporting burden of the final rule, providing estimates for those safety reports not already approved under OMB control number 0910–0014.

TABLE 6.—ESTIMATED ANNUAL REPORTING BURDEN OF THE FINAL RULE[1]

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Hours per Response	Total Hours
320.31(d) Bioavailability and Bioequivalence Safety Reports	10	20	200	14	2,800
312.32(c)(1)(ii) and (c)(1)(iii) IND Safety Reports[2]	100	6	600	12	7,200
312.32(c)(1)(iv) IND Safety Reports[3]	10	1	10	12	120

[1] There are no capital costs or operating and maintenance costs associated with this collection. The estimates are for the additional burdens beyond those already approved for then-current §§ 312.32 and 312.64.

[2] Includes reports based on findings suggesting a significant risk in humans from epidemiological studies, pooled analysis of multiple studies, other clinical studies, or in vitro testing. Reports from animal testing are not included (see footnote 3 of this document).

[3] Includes reports of clinically important increases in the rate of occurrence of serious suspected adverse reactions over that listed in the protocol or investigator brochure.

The information collection provisions of this final rule have been submitted to OMB for review. Prior to the effective date of this final rule, FDA will publish a notice in the **Federal Register** announcing OMB's decision to approve, modify, or disapprove the information collection provisions in this final rule. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

VIII. Executive Order 13132: Federalism

FDA has 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 final 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.

IX. References

The following references have been placed on display in the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. (FDA has verified the Web site addresses, but FDA is not responsible for any subsequent changes to the Web sites after this document publishes in the **Federal Register**.)

1. Enterprise Directorate-General, European Commission, "Detailed Guidance on the Collection, Verification and Presentation of Adverse Reaction Reports Arising From Clinical Trials on Medicinal Products for Human Use," revision 2, Brussels, ENTR/CT 3, April 2006 (*http://ec.europa.eu/enterprise/index_en.htm*).

2. Council for International Organizations of Medical Sciences, "Guidelines for Preparing Core Clinical-Safety Information on Drugs. Second Edition, Including New Proposals for Investigator's Brochures," Report of CIOMS Working Groups III and V, Geneva, 1999.

3. Council for International Organizations of Medical Sciences, "Management of Safety Information From Clinical Trials," Report of CIOMS Working Group VI, Geneva, 2005.

4. U.S. Department of Labor, Bureau of Labor Statistics, National Industry-Specific Occupational Employment and Wage Estimates. NAICS 325400 - Pharmaceutical and Medicine Manufacturing, May 2007, extracted September 3, 2008, *http://www.bls.gov/oes/current/naics4_325400.htm*.

5. U.S. Department of Commerce, Bureau of the Census, Economic Census, Manufacturing Industry Series, Pharmaceutical Preparation Manufacturing, Table 4, EC02–311–325412 (RV), 2002.

6. U.S. Department of Commerce, Bureau of the Census, Economic Census, Manufacturing Industry Series, Biological Product Manufacturing, Table 4, EC02–311–325414 (RV), 2002.

List of Subjects

21 CFR Part 312

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

21 CFR Part 320

Drugs, Reporting and recordkeeping requirements.

■ 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 parts 312 and 320 are amended as follows:

PART 312— INVESTIGATIONAL NEW DRUG APPLICATION

■ 1. The authority citation for 21 CFR part 312 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360bbb, 371; 42 U.S.C. 262.

■ 2. Section 312.32 is revised to read as follows:

§ 312.32 IND safety reporting.

(a) *Definitions.* The following definitions of terms apply to this section:

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Life-threatening adverse event or *life-threatening suspected adverse reaction.* An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse event or *serious suspected adverse reaction.* An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require

medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Unexpected adverse event or *unexpected suspected adverse reaction.* An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

(b) *Review of safety information.* The sponsor must promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from foreign or domestic sources, including information derived from any clinical or epidemiological investigations, animal or in vitro studies, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities and reports of foreign commercial marketing experience for drugs that are not marketed in the United States.

(c)(1) *IND safety reports.* The sponsor must notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting under paragraph (c)(1)(i), (c)(1)(ii), (c)(1)(iii), or (c)(1)(iv) of this section. In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction, and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information.

(i) *Serious and unexpected suspected adverse reaction.* The sponsor must report any suspected adverse reaction that is both serious and unexpected. The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:

(A) A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);

(B) One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);

(C) An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

(ii) *Findings from other studies.* The sponsor must report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies (other than those reported under paragraph (c)(1)(i) of this section), whether or not conducted under an IND, and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug. Ordinarily, such a finding would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.

(iii) *Findings from animal or in vitro testing.* The sponsor must report any findings from animal or in vitro testing, whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity at or near the expected human exposure. Ordinarily, any such findings would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.

(iv) *Increased rate of occurrence of serious suspected adverse reactions.* The sponsor must report any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure.

(v) *Submission of IND safety reports.* The sponsor must submit each IND safety report in a narrative format or on FDA Form 3500A or in an electronic format that FDA can process, review, and archive. FDA will periodically issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files). The sponsor may submit foreign suspected adverse reactions on a Council for International Organizations of Medical Sciences (CIOMS) I Form instead of a FDA Form 3500A. Reports of overall findings or pooled analyses from published and unpublished in vitro, animal, epidemiological, or clinical studies must be submitted in a narrative format. Each notification to FDA must bear prominent identification of its contents, i.e., "IND Safety Report," and must be transmitted to the review division in the Center for Drug Evaluation and Research or in the Center for Biologics Evaluation and Research that has responsibility for review of the IND. Upon request from FDA, the sponsor must submit to FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

(2) *Unexpected fatal or life-threatening suspected adverse reaction reports.* The sponsor must also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

(3) *Reporting format or frequency.* FDA may require a sponsor to submit IND safety reports in a format or at a

frequency different than that required under this paragraph. The sponsor may also propose and adopt a different reporting format or frequency if the change is agreed to in advance by the director of the FDA review division that has responsibility for review of the IND.

(4) *Investigations of marketed drugs.* A sponsor of a clinical study of a drug marketed or approved in the United States that is conducted under an IND is required to submit IND safety reports for suspected adverse reactions that are observed in the clinical study, at domestic or foreign study sites. The sponsor must also submit safety information from the clinical study as prescribed by the postmarketing safety reporting requirements (e.g., §§ 310.305, 314.80, and 600.80 of this chapter).

(5) *Reporting study endpoints.* Study endpoints (e.g., mortality or major morbidity) must be reported to FDA by the sponsor as described in the protocol and ordinarily would not be reported under paragraph (c) of this section. However, if a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis), the event must be reported under § 312.32(c)(1)(i) as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (e.g., all-cause mortality).

(d) *Followup.* (1) The sponsor must promptly investigate all safety information it receives.

(2) Relevant followup information to an IND safety report must be submitted as soon as the information is available and must be identified as such, i.e., "Followup IND Safety Report."

(3) If the results of a sponsor's investigation show that an adverse event not initially determined to be reportable under paragraph (c) of this section is so reportable, the sponsor must report such suspected adverse reaction in an IND safety report as soon as possible, but in no case later than 15 calendar days after the determination is made.

(e) *Disclaimer.* A safety report or other information submitted by a sponsor under this part (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the sponsor or FDA that the report or information constitutes an admission that the drug caused or contributed to an adverse event. A sponsor need not admit, and may deny, that the report or information submitted by the sponsor constitutes an admission that the drug caused or contributed to an adverse event.

■ 3. Section 312.64 is amended by revising paragraph (b) to read as follows:

§ 312.64 Investigator reports.

* * * * *

(b) *Safety reports.* An investigator must immediately report to the sponsor any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor. The investigator must record nonserious adverse events and report them to the sponsor according to the timetable for reporting specified in the protocol.

* * * * *

PART 320—BIOAVAILABILITY AND BIOEQUIVALENCE REQUIREMENTS

■ 4. The authority citation for 21 CFR part 320 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 355, 371.

■ 5. Section 320.31 is amended in paragraphs (d)(1) and (d)(2) by removing the word "shall" and by adding in its place the word "must," and by removing "and" at the end of paragraph (d)(1) and replacing "this chapter." at the end of paragraph (d)(2) with "this chapter; and", and by adding paragraph (d)(3) to read as follows:

§ 320.31 Applicability of requirements regarding an "Investigational New Drug Application."

* * * * *

(d) * * *

(3) The person conducting the study, including any contract research organization, must notify FDA and all participating investigators of any serious adverse event, as defined in § 312.32(a), observed during the conduct of the study as soon as possible but in no case later than 15 calendar days after becoming aware of its occurrence. Each report must be submitted on FDA Form 3500A or in an electronic format that FDA can process, review, and archive. FDA will periodically issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files). Each report must bear prominent identification of its contents, i.e., "bioavailability/bioequivalence safety report." The person conducting the study, including any contract research organization, must also notify FDA of any fatal or life-threatening adverse event from the study as soon as possible but in no case later than 7 calendar days after becoming aware of its occurrence. Each notification under this paragraph must be submitted to the Director, Office of Generic Drugs in the Center for Drug Evaluation and Research at FDA. Relevant followup information to a bioavailability/bioequivalence safety report must be submitted as soon as the information is available and must be identified as such, i.e., "Followup bioavailability/bioequivalence safety report." Upon request from FDA, the person conducting the study, including any contract research organization, must submit to FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

Dated: September 23, 2010.

Leslie Kux,

Acting Assistant Commissioner for Policy.

[FR Doc. 2010–24296 Filed 9–28–10; 8:45 am]

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DEPARTMENT OF HOMELAND SECURITY

Coast Guard

33 CFR Part 165

[Docket No. USCG–2010–0620]

RIN 1625–AA00

Safety Zone: Monte Foundation Firework Display, Monterey, CA

AGENCY: Coast Guard, DHS.

ACTION: Temporary final rule.

SUMMARY: The Coast Guard is establishing a temporary safety zone in the navigable waters of Monterey Bay off the fishing pier of Seacliff State Beach, Santa Cruz, CA in support of the Monte Foundation Firework Display. This safety zone is established to ensure the safety of participants and spectators from the dangers associated with the pyrotechnics. Unauthorized persons and vessels are prohibited from entering into, transiting through, or remaining in the safety zone without permission from the Captain of the Port or her designated representative.

DATES: This rule is effective from 7 a.m. through 9:30 p.m. on October 8, 2010.

ADDRESSES: Documents indicated in this preamble as being available in the docket are part of docket USCG–2010–0620 and are available online by going