paragraphs (b)(4)(i) through (iv) of this section and does not present a potential for significant risk to the health, safety, or welfare of the subjects. If FDA grants such an exemption, we will notify the sponsor or sponsor-investigator of the exemption in writing. The exemption will become effective when the sponsor or sponsor-investigator receives written notification that we have granted the exemption.

(v) FDA may revoke an exemption granted under paragraph (b)(5)(iii) or (iv) of this section if we become aware of information suggesting that the clinical investigation could present a potential for significant risk to the health, safety, or welfare of subjects, or that the investigation does not meet any requirement in paragraphs (b)(4)(i) through (iv) of this section. FDA will notify the sponsor or sponsor-investigator who received the exemption of the reason for revoking the exemption and, if appropriate, may direct the sponsor or sponsor-investigator to suspend the investigation and/or cease recruiting new subjects to the investigation.

(6) FDA will not accept an application for an investigation that is exempt under the provisions of paragraph (b)(1), (b)(4), or (b)(5) of this section.

* * * * *

Dated: November 28, 2022.

Robert M. Califf,

Commissioner of Food and Drugs.

[FR Doc. 2022–26728 Filed 12–8–22; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 312

[Docket No. FDA–2020–N–0258]

RIN 0910–AI37

Investigational New Drug Application Annual Reporting

AGENCY: Food and Drug Administration, Department of Health and Human Services (HHS).

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA, the Agency, or we) is proposing to replace its current annual reporting requirement for investigational new drug applications (INDs) with a new requirement: the annual FDA development safety update report (FDA DSUR). The proposed annual FDA DSUR is intended to be consistent with the format and content of the DSUR that is supported by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), which is described in FDA's ICH guidance for industry entitled ''E2F Development Safety Update Report'' (E2F DSUR) (August 2011). The proposed annual FDA DSUR regulation, if finalized, would require an annual report that is more comprehensive and informative than the IND annual report currently required under FDA regulations.

DATES: Submit either electronic or written comments on the proposed rule by March 9, 2023. Submit comments on information collection issues under the Paperwork Reduction Act of 1995 (PRA) by January 9, 2023.

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. The *https://www.regulations.gov* electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of March 9, 2023. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

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

Written/Paper Submissions

Submit written/paper submissions as follows:

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

Instructions: All submissions received must include the Docket No. FDA–2020–N–0258 for ''Investigational New Drug Application Annual Reporting.'' Received comments, those filed in a timely manner (see **ADDRESSES**) will be placed in the docket and, except for those submitted as ''Confidential Submissions,'' publicly viewable at *https://www.regulations.gov* or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions—To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states ''THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.'' The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on *https://www.regulations.gov.* Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as ''confidential.'' Any information marked as ''confidential'' will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: *https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.*

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to *https://*

www.regulations.gov and insert the docket number, found in brackets in the heading of this document, into the ''Search'' box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

Submit comments on information collection issues under the PRA to the Office of Management and Budget (OMB) in the following ways:

- Fax to the Office of Information and Regulatory Affairs, OMB, Attn: FDA Desk Officer, Fax: 202–395–7285, or email to *oira_submission@omb.eop.gov*. All comments should be identified with the title, ''Investigational New Drug Application Annual Reporting.''

FOR FURTHER INFORMATION CONTACT:

With regard to the proposed rule: Dat Doan, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 3334, Silver Spring, MD 20993–0002, 240–402–8926, *Dat.Doan@fda.hhs.gov; or* Stephen Ripley, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 7301, Silver Spring, MD 20993–0002, 240–402–7911, *Stephen.Ripley@fda.hhs.gov.*

With regard to the information collection: Domini Bean, Office of Operations, Food and Drug Administration, Three White Flint North 10A–12M, 11601 Landsdown St., North Bethesda, MD 20852, 301–796–5733, *PRAStaff@fda.hhs.gov*.

SUPPLEMENTARY INFORMATION:

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I. Executive Summary

A. Purpose of the Proposed Rule

FDA is proposing to replace the current annual reporting requirement under § 312.33 (21 CFR 312.33), Annual reports, with a new requirement under § 312.33, Development safety update reports. Current § 312.33 requires sponsors that have an IND in effect to submit an annual report that must contain individual study information, which generally includes brief summaries of the status of each ongoing study and of each study completed during the previous year. The proposed annual FDA DSUR regulation would require these sponsors to provide an annual report that is more comprehensive and informative than the IND annual report currently required under FDA regulations—such as the requirement for an integrated overall safety analysis and a summary of cumulative pertinent safety information. In light of the increasing complexity of clinical studies, requiring a DSUR that offers a more comprehensive and informative assessment of risk than the current annual report would provide an important tool for FDA and sponsors to identify and manage potential risks and therefore reduce exposure of human subjects to unnecessary risks. Furthermore, because FDA intends that the DSUR be consistent with the format and content of submission of the DSUR supported by ICH, the annual reporting process for sponsors would be more efficient by supporting one format for submission to FDA and multiple regulatory authorities in the European Union (EU) and other countries and regions. This action is consistent with FDA's overarching goal of fostering international harmonization of regulatory requirements to the extent appropriate and feasible. If ICH updates its DSUR guidelines, FDA may evaluate the proposed regulation to determine if any corresponding updates are necessary.

B. Summary of the Major Provisions of the Proposed Rule

The following is a brief summary of the proposed revisions to the current requirements for IND annual reporting that are made by the proposed annual FDA DSUR regulation:

- Expands the scope to require comprehensive information and allow for a thorough assessment by FDA of clinical investigations conducted anywhere in the world on behalf of the sponsor evaluating the drug (proposed § 312.33(a)(1)).
- Provides that a sponsor-investigator for a clinical investigation that is not intended to support a marketing application is only required to submit information obtained from that clinical investigation (*e.g.,* information that is part of that sponsor-investigator's protocol for the IND) (proposed § 312.33(a)(2)).
- Requires an executive summary (proposed § 312.33(c)).
- Requires a description of all actions relevant to the safety of the drug that were taken during the reporting period by any regulatory authority or by the sponsor, if known (proposed § 312.33(g)).
- Provides that the investigator brochure would serve as the reference safety information during the reporting period. If a sponsor is not required to submit an investigator brochure, the FDA-approved prescribing information would serve as the reference safety information. If the sponsor uses another source as the reference safety information, the regulation would require the sponsor to identify the reference safety information used (proposed § 312.33(h)(1)).
- Requires sponsors to provide a list of all safety-related changes to the reference safety information, if applicable, for the investigational drug during the reporting period. (proposed § 312.33(h)(2)).
- Requires that the report provide the clinical trial phase, the date the first participant provided informed consent, a brief description of the clinical investigation, and a brief description of the dose and regimen of the investigational drug and any comparators as part of an inventory of clinical investigations conducted during the reporting period. Also expands the requirement for information on study subjects to include the cumulative number of subjects enrolled in all treatment arms of each clinical investigation (or an estimate), the countries or regions in which each investigation was conducted, and the total number of subjects planned to be enrolled in each clinical investigation (proposed § 312.33(i)).
- Adds the requirement to include the cumulative number of subjects exposed to the investigational drug and comparators during clinical investigations that are conducted on behalf of the sponsor (proposed § 312.33(j)).
- Adds the requirement that sponsors provide line listings of all *serious suspected adverse reactions* (as defined in § 312.32(a)) that occurred during the reporting period, including treatment assignment. Adds the requirement that

the line listings of all serious suspected adverse reactions identify those that are unexpected (serious and unexpected suspected adverse reaction) as defined in § 312.32(a).

- Adds the requirement to include a cumulative summary tabulation of *serious adverse events* (as defined in § 312.32(a)) obtained from all clinical investigations conducted on behalf of the sponsor that occurred since the date the IND went into effect (proposed § 312.33(k)(1)(ii)).
- Requires identifying each event omitted from the listings and tabulations of safety data required under proposed § 312.33(k)(1) because the event is a study endpoint or a component of a study endpoint (proposed § 312.33(k)(2)).
- Requires a brief summary of safety and effectiveness findings from clinical investigations of the investigational drug conducted on behalf of the sponsor that are obtained during the reporting period (proposed § 312.33(l)).
- Adds the requirement that the sponsor submit a brief summary of key safety findings obtained from other sources during the reporting period (proposed § 312.33(m)).
- Requires sponsors to provide a summary of significant chemistry, manufacturing, and control changes, including microbiological changes (if applicable), made to the investigational drug during the reporting period, as well as a brief description of the safety significance of the identified changes (proposed § 312.33(n)).
- Requires a concise, integrated evaluation of all new clinical, nonclinical, and epidemiological safety information obtained about the drug by the sponsor during the reporting period relative to the sponsor's prior knowledge of the drug (proposed § 312.33(s)).
- Requires providing a cumulative listing and brief description of all important known risks and potential risks associated with the use of the drug identified by the sponsor throughout the course of studies of the drug conducted on behalf of the sponsor (proposed § 312.33(t)).
- Requires a conclusion that briefly summarizes changes to the sponsor's previous knowledge of the investigational drug's efficacy and safety resulting from information obtained during this reporting period, in addition to an outline of actions by the sponsor that have been taken during the current reporting or will be taken in the future to address emerging safety findings (proposed § 312.33(u)).

C. Legal Authority

FDA is issuing this proposed rule under sections 201, 301, 501, 502, 503, 505, and 701 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 321, 331, 351, 352, 353, 355, and 371) and under section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262).

D. Costs and Benefits

The estimated benefits would result from savings in labor costs for sponsors who may no longer have to prepare a different type of periodic safety report for submission to certain other countries or regions in which a drug might be studied. Moreover, FDA would receive safety data on investigational new drugs that is more comprehensive, which would enhance our ability to oversee the progress and safety of clinical investigations. The estimate of annualized benefits over 10 years ranges from $47.86 million to $117.99 million with a primary value of $86.46 million at a 7 percent discount rate and from $49.24 million to $121.01 million with a primary value of $88.79 million at a 3 percent discount rate. The primary estimate of the present value of benefits over 10 years is $607.29 million at a 7 percent discount rate and $757.38 million at a 3 percent discount rate. Costs would arise from increased labor associated with preparing and submitting a periodic safety report that is more comprehensive to meet the proposed requirements. Costs to government would arise from increased FDA resources being used to review the more comprehensive report. The estimate of annualized costs over 10 years ranges from $40.43 million to $101.34 million at a 7 percent discount rate with a primary value of $61.11 million. Using a 3 percent discount rate, the annualized costs range from $40.89 million to $102.48 million with a primary value of $61.81 million. The primary estimate of the present value of costs over 10 years is $429.20 million at a 7 percent discount rate and $527.21 million at a 3 percent discount rate.

II. Table of Abbreviations/Commonly Used Acronyms in This Document

Abbreviation/acronym	What it means
CBER	Center for Biologics Evaluation and Research.
CDER	Center for Drug Evaluation and Research.
CIOMS	Council for International Organizations of Medical Sciences.
DMC	Data Monitoring Committee.
DSUR	Development Safety Update Report.
E2F DSUR	E2F Development Safety Update Report (guidance for industry).
EU	European Union.
FDA	Food and Drug Administration.
FDA DSUR	FDA Development Safety Update Report.
ICH	International Council for Harmonisation.
IND	Investigational New Drug Application.
OMB	Office of Management and Budget.
PHS	Public Health Service.
PRA	Paperwork Reduction Act of 1995.

III. Background

A. Introduction

FDA is proposing to replace the current annual reporting requirement with a new annual reporting requirement. The proposed action would require IND sponsors to submit an annual FDA DSUR—a report that retains the general aspects of the current annual report but includes information that is more comprehensive and is generally consistent with the format and content of the E2F DSUR (available at *https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e2f-development-safety-update-report*). The proposed annual FDA DSUR is similar to the annual safety reporting requirements in certain other countries and regions in which a drug might be studied. Promulgation of a rule containing requirements that are similar to the DSUR recommendations developed by ICH (see E2F DSUR) is also consistent with FDA's overarching goal of fostering international

harmonization of regulatory requirements to the extent appropriate and feasible. Therefore, FDA expects that some of the additional regulatory burden associated with preparing a report for FDA that is more comprehensive than previously required will be offset by the mitigation of the previous regulatory burden on those sponsors who submit multiple different reports to regulatory authorities in other countries or regions.

B. Need for the Regulation

FDA is proposing this action because of the advantages that the proposed annual FDA DSUR would provide over the current IND annual report. The advantages include: (1) enabling FDA to more efficiently identify and review new safety signal information; (2) creating a more efficient reporting process for certain sponsors by supporting a more comprehensive format for submission to FDA and multiple regulatory authorities worldwide; and (3) allowing regulatory authorities worldwide to have access to the same data within the same timeframes. For example, the DSUR includes a section that tracks knowledge about each specific safety issue through time, facilitating efficient identification and review of any new safety signal information. The integration of data from a development program with postmarketing data provides a powerful means to facilitate identification and review of any new safety signals. As discussed in section III.D.3, the proposed annual FDA DSUR will provide a more comprehensive and detailed safety summary than the IND annual report, which will facilitate reviewers' ability to efficiently identify and review new safety signal information.

The proposed annual FDA DSUR would better capture and characterize the evolving safety profile of the investigational drug and would better describe new safety findings that could have an impact on the protection of study subjects. Simply accumulating and reporting data for a given time period, as required under the current IND annual report, without considering all previously available data from clinical trials and other sources, may delay identification of important risks. DSURs specifically include a section that tracks knowledge about each specific safety issue through time, facilitating efficient identification and review of any new safety signal information.

Furthermore, a requirement for investigational drug reporting similar to the reporting done in the EU could help sponsors who need to satisfy annual reporting requirements in different countries and regions and would help prevent sponsors from sending duplicative information in different formats to different regulatory authorities. A similar annual reporting requirement would also help provide authorities in different countries with a common description of the evolving safety profile of a drug, and thus, could help ensure greater consistency and predictability in regulatory actions. We expect that the proposed annual FDA DSUR would help harmonize FDA's requirements for IND annual reporting with the E2F DSUR.

We have received support for the proposed annual FDA DSUR through public comments submitted in response to documents published in the **Federal Register**. For example, in response to a request for public comment in the **Federal Register** of April 27, 2011 (76 FR 23520), a trade organization representing major biotechnology companies urged FDA to update its regulations to reflect current practice and to be consistent with the language in the E2F DSUR. (See Docket No. FDA–2011–N–0259.) In the **Federal Register** of August 5, 2008 (73 FR 45462), FDA requested public comment on the E2F DSUR draft guidance for industry. In response, FDA received comments from pharmaceutical manufacturers and a trade association. (See Docket No. FDA–2008–D–0386.) Some comments proposed certain modifications to the DSUR as described in the draft guidance but were generally supportive of the draft guidance and noted that the use of the E2F DSUR would help harmonize annual reporting of clinical trials, thus enhancing efficiency and providing regulators, investigators, patients, and industry with valuable, consolidated safety information. Other comments expressed a preference for the use of the E2F DSUR to minimize discrepancies, which are, at the present time, common in the information different regulators receive. Taken together, the public comments expressed support for requiring a single reporting format for periodic safety reporting under an IND and a preference for use of the format, content, and timing of the E2F DSUR.

C. FDA's Current Regulatory Framework

1. IND Regulations

The IND regulations in part 312 contain procedures and requirements governing the use of investigational drugs, including biological products that do not also meet the definition of *device* under the FD&C Act (s*ee* 21 U.S.C. 321(g) through (h), 42 U.S.C. 262(i) through (j); *see also* 21 CFR 601.21) and contain procedures and requirements for the submission of INDs to FDA and for FDA's review of those INDs. Under the IND regulations in part 312, sponsors are required to have an IND in effect to support the use of an investigational drug in clinical trials or for expanded access uses. The IND regulations also provide various mechanisms for continued FDA oversight of clinical investigations conducted under an IND. The IND annual report currently required under § 312.33 is intended to serve as the means for reporting the status of studies being conducted under the IND and for providing the general investigational plan and safety-related changes to the investigational plan for the coming year. This proposed rule focuses on § 312.33, Annual report.

2. FDA's IND Annual Report

In the **Federal Register** of March 19, 1987 (52 FR 8798, as amended at 52 FR 23031, June 17, 1987; 63 FR 6854, February 11, 1998; and 67 FR 9584, March 4, 2002), FDA published regulations for new drug, antibiotic, and biologic drug products as part of an overall revision of the IND regulations (known as the IND Rewrite). These regulations, in part, require each sponsor to submit an annual report providing an update on the progress of clinical investigations conducted under its IND. The annual report must contain individual study information, which generally includes brief summaries of the status of each ongoing study and of each study completed during the previous year. These summaries are required to include, among other things: (1) a brief description of available results of each study completed during the previous year and interim results of ongoing clinical investigations and (2) information on the number of subjects included in each study (see § 312.33(a)). The annual report must also include summarized information about the clinical investigations conducted under the IND during the previous year, including the following, for example:

- A summary showing the most frequent and most serious adverse experiences (§ 312.33(b)(1)).
- A summary of all IND safety reports submitted during the previous year (§ 312.33(b)(2)).
- A list of preclinical studies completed or in progress during the previous year, including a summary of the major preclinical findings (§ 312.33(b)(6)).
- A summary of any significant manufacturing or microbiological

changes made during the past year (§ 312.33(b)(7)).

Since the publication of the IND Rewrite, the increasing size and scope of clinical investigations have created the need for information and analyses that are more comprehensive, as well as the need for information to be presented in a format that is more useful for FDA, clinical investigators, sponsors, and others using the data included in the reports. Such comprehensive analyses will assist FDA in evaluating the safety profile of an investigational drug during its development and will assist in identifying safety signals while the clinical trials are ongoing. Because of the increasing complexity of clinical trials, having periodic reporting and consistent information reported are of increased importance for protecting human subjects from unnecessary risks. Additionally, there have been concerns about differences in the content and objectives between the current IND annual report and the annual safety report that is being used in other countries, as well as concerns about the burden associated with preparing different periodic safety reports for different regulatory authorities. These concerns led to an international effort to develop a common periodic safety report that could be used globally to satisfy reporting requirements.

D. History of the Rulemaking

1. International Harmonization of Regulatory Requirements for Drug Development

In the **Federal Register** of October 11, 1995 (60 FR 53078), FDA published a notice entitled ''International Harmonization, Policy on Standards'' that described FDA's policy for working with other countries to achieve greater harmonization of regulatory requirements and guidelines. It also described FDA's views on international harmonization and collaboration as a way to enhance regulatory effectiveness by providing more consumer protection without added expenditure of government resources. Harmonization and collaboration can also increase worldwide consumer access to safe, effective, and high-quality products.

International harmonization has been facilitated through the development of ICH guidelines via a process of scientific consensus with regulatory and industry experts participating in multinational working groups. In 2006, the Center for Biologics Evaluation and Research (CBER) and the Center for Device Evaluation and Research (CDER) participated in a working group sponsored by the Council for International Organizations of Medical Sciences (CIOMS), referred to as CIOMS VII (Ref. 1). CIOMS is an international, nongovernmental, nonprofit organization established by the World Health Organization and the United Nations Educational, Scientific, and Cultural Organization that covers drug safety topics through working groups (Refs. 2 and 3). The CIOMS VII working group proposed that ICH develop a guideline on periodic reporting of safety information from clinical trials (which it termed the development safety update report (DSUR)) that would harmonize guidelines and requirements from the various regulatory agencies (Ref. 1).

2. Development of an International DSUR

The CIOMS report was the starting point for the ICH initiative (Ref. 4). In June 2008, the draft ICH guideline for the E2F DSUR was approved by the ICH steering committee (Ref. 5). In the **Federal Register** of August 5, 2008, FDA announced the availability of the draft ICH guidance for industry (E2F DSUR) (available at *https://www.regulations.gov/document?D=FDA-2008-D-0386-0002)* for public comment, which was the guideline prepared under the auspices of the ICH. After consideration of the comments received on the draft guidance for industry, the ICH steering committee approved a final draft of the guideline to be adopted by the United States, Japan, and participating European countries entitled ''Development Safety Update Report, E2F,'' dated August 17, 2010 (Ref. 5). In the **Federal Register** of August 23, 2011 (76 FR 52667), FDA issued this guideline as a final ICH guidance for industry (the E2F DSUR) that discusses the format, content, and timing of submission of a DSUR as developed by the ICH.

3. Overview of the Differences Between the E2F DSUR and the Current IND Annual Report Regulations

The E2F DSUR provides the recommended content and format of a drug safety update report that sponsors can use to satisfy the EU requirements for annual safety reports and FDA's requirements for IND annual reports, despite the differences between the EU requirements and FDA's requirements. Specifically, the annual safety report required under the EU Clinical Trial Directive 2001/20EC contains significant differences in the purpose, content, and timing of submission compared to FDA's IND annual report (Refs. 6 and 7). As a result, sponsors developing a drug in both jurisdictions are required to submit different annual reports each year to each regulatory authority. For example, the IND annual report is intended to provide only summaries of clinical studies conducted under the IND and requires a narrative or tabular summary of the most frequent and most serious adverse experiences. In contrast, the EU annual safety report is intended to be a clinical trial safety report and requires a cumulative summary tabulation of all serious adverse reactions (Refs. 6 and 7). With regard to timing, the required date for submission of the IND annual report is based on the anniversary of the effective date of the IND under § 312.40(b), whereas the date for submission of the EU annual safety report is the anniversary of the development international birth date, which is the date on which the sponsor was first authorized to conduct a clinical trial in any country or region (Ref. 1). The differences in the purpose, content, and timing of annual reporting in the EU and the United States result in study sponsors sending duplicative information to regulators, as well as regulatory authorities receiving inconsistent safety information.

The E2F DSUR provides recommendations with respect to periodic safety reporting during clinical development, offers guidance on providing meaningful information to regulators, and facilitates consistency among sponsors and regulators (Ref. 4). The E2F DSUR emphasizes high-value activities, such as data interpretation, while ensuring that the regulatory authorities that use the E2F DSUR have access to the same data in similar timeframes (Ref. 4). Following are overarching objectives enabled by the use of the E2F DSUR:

- Examining whether the information obtained by the sponsor during the reporting period aligns with prior knowledge of the safety of the investigational drug.
- Describing new safety findings that could have an impact on the protection of study subjects.
- Summarizing the current understanding and management of identified and potential risks.
- Providing an update on the status of the clinical investigation/development program and study results.

Use of the E2F DSUR provides important advantages for safety evaluation as compared to FDA's IND annual report. First, the E2F DSUR includes additional safety information to help enhance the safety of subjects. For example, the E2F DSUR specifically includes a description of significant, safety-related changes to the investigator

brochure and an evaluation of the significance of the identified changes for the safety of subjects. For some drugs, this increased safety reporting requirement could potentially help characterize a safety signal and associated risks, and lead to timely action to protect subjects such as earlier termination of a study or withdrawal of a drug from the market due to safety concerns (as mentioned previously). In contrast, the IND annual report is a general update on the progress of the investigational drug's clinical development, which includes a description of the revisions made to the investigator brochure and a copy of the new brochure, if revised, and a summary of all IND safety reports submitted during the year, but no additional analysis is conducted by the sponsor.

Second, unlike FDA's IND annual report, the E2F DSUR contains an integrated safety analysis and a summary of cumulative pertinent safety information. Simply accumulating and reporting data for a given time period, without considering all previously available data from clinical trials and other sources, may delay identification of important risks. A meaningful understanding of the evolving safety profile of an investigational drug requires a periodic analysis of all available safety information, which is crucial to the ongoing assessment of risks to subjects of clinical trials during the clinical development of an investigational drug. An integrated analysis and a summary of overall safety risks, as contained in the E2F DSUR, would help increase the usefulness of the safety data and help facilitate efforts to identify and assess important safety risks promptly. The E2F DSUR includes information on cumulative patient exposure and a summary of cumulative serious adverse events, which would further enhance risk identification and assessment.

Third, the E2F DSUR provides safety information that is more comprehensive than the IND annual report, which requires only summaries of clinical studies conducted under the IND. In contrast to the current IND annual report, the E2F DSUR contains safety information from all studies using the drug, whether conducted under an IND or not. The E2F DSUR also incorporates information from studies not initiated by the sponsor and information from other relevant sources. For example, safety findings from published literature and information from the marketing experience of the drug would be included in the E2F DSUR, but these findings are not required in the IND annual report. Some sponsors have already voluntarily submitted their IND annual reports in the E2F DSUR format to the FDA; the submitted E2F DSURs have provided the aforementioned advantages, including superior organization and more comprehensive information to facilitate review.

Finally, the ability to submit a similar annual report to regulatory authorities in multiple countries and for all investigations of the drug conducted on behalf of the sponsor could provide significant advantages to those sponsors who submit reports to multiple regulatory authorities. A similar comprehensive annual report submitted to regulatory authorities in multiple countries could help ensure consistent understanding of the safety profile of a drug and could therefore help improve consistency and predictability of regulatory actions. The use of a similar annual report in multiple countries and for all studies conducted on behalf of the sponsor in which the particular drug is studied also could help ensure that regulatory authorities for all development programs are relying on the same information about the evolving safety profile of a drug.

IV. Legal Authority

FDA is issuing this proposed rule under sections 201, 301, 501, 502, 503, 505, and 701 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 321, 331, 351, 352, 353, 355, and 371) and under section 351 of the PHS Act.

V. Description of the Proposed Rule

A. Scope

The proposed rule would revise current §§ 312.3 and 312.33 concerning IND annual reports. The proposed rule would require IND sponsors to submit an annual DSUR that is more comprehensive and informative than the IND Annual Report currently required under FDA regulations. The proposed annual FDA DSUR is intended to be consistent with the format and content of the E2F DSUR supported by ICH for annual reporting in certain other countries and regions. If finalized, this rule would require sponsors to submit an annual FDA DSUR in lieu of the IND Annual Report. A sponsor would be able to submit an annual DSUR containing additional information to that proposed to be required by the annual FDA DSUR, in the format recommended in the E2F DSUR, as long as the submitted DSUR complies with the requirements provided in the proposed annual FDA DSUR and FDA requirements for electronic submissions (see, *e.g.,* section 745A(a) of the FD&C Act (21 U.S.C. 379k–1)(a)). The proposed requirements are intended to provide information that is sufficiently comprehensive to facilitate FDA's assessment of clinical investigations conducted on behalf of the IND sponsor, including the sponsor of a large, multinational clinical development program intended to support applications for marketing approval of a drug in multiple countries and regions.

B. Definitions

The proposed rule would revise § 312.3 (Definitions and interpretations) by adding a definition for *data lock point.* The data lock point would be defined as the designated cutoff date for data to be included in the proposed annual FDA DSUR. The definition would establish a fixed data lock point that is 1 calendar day before the anniversary of the date the IND went into effect. We propose to require that a sponsor submit the annual FDA DSUR to FDA not later than 60 calendar days after the data lock point (see proposed § 312.33).

C. Proposed Provisions of the FDA DSUR

1. General

FDA is proposing to revise current § 312.33, Annual reports, by replacing the section with a section entitled ''Development safety update reports.'' Proposed § 312.33 describes the scope, format, and content of the proposed annual FDA DSUR as well as when to submit the annual report. The proposed requirements are intended to be consistent with the content recommended in the E2F DSUR to the extent possible. Some of the language used in this proposed rule differs from that in the E2F DSUR because of minor differences in terminology and for consistency with other FDA requirements. We recognize that some of the information discussed in the proposed annual FDA DSUR may not be known to sponsors, which is why the proposed annual FDA DSUR only requires sponsors to submit the information that is known to them.

2. Scope

Proposed § 312.33(a) states that the annual FDA DSUR is intended to provide a thorough annual assessment of the clinical investigations conducted and safety information collected during the reporting period that is related to an investigational new drug. The annual FDA DSUR is intended to: (1) be sufficiently comprehensive to cover the entire scope of a large-scale, international development program

designed to support applications for marketing in multiple countries and regions and (2) capture data from all completed and ongoing clinical investigations conducted on behalf of the sponsor anywhere in the world evaluating the drug, including investigations not conducted under an IND (see § 312.33(a)(1)). Proposed § 312.33(a)(1) further provides that a sponsor must submit the same annual FDA DSUR for each IND held by the sponsor for that drug.

Under § 312.10, sponsors may request that FDA waive any applicable requirement in part 312. We expect that some sponsors will request that FDA waive the requirement under proposed § 312.33 that they must submit the annual FDA DSUR not later than 60 calendar days after a *data lock point* established by proposed § 312.3 (which is 1 calendar day before the anniversary of the date the IND went into effect) to allow them to coordinate the timing of the annual FDA DSUR submission with the submission of reports to regulatory agencies in other countries or regions. We also expect that some sponsors will request that FDA waive the requirement under proposed § 312.33(a)(1) that a sponsor submit the same annual FDA DSUR for each IND held by the sponsor for the drug because of substantial differences in, for example, the intended uses or populations being studied under different INDs.

As required under § 312.10(a), a waiver request must contain the following: (1) an explanation of why the sponsor's compliance with the requirement is unnecessary or cannot be achieved, (2) a description of an alternative submission or course of action that satisfies the purpose of the requirement, or (3) other information that justifies a waiver. As provided under § 312.10(b), FDA may grant a requested waiver if it finds that the sponsor's noncompliance would not pose a significant and unreasonable risk to human subjects of the investigation and that at least one of the following is met: (1) the sponsor's compliance with the requirement is unnecessary for the Agency to evaluate the application or compliance cannot be achieved, (2) the sponsor's proposed alternative satisfies the requirement, or (3) the applicant's submission otherwise justifies a waiver.

FDA expects that the waiver criteria in § 312.10(b) will likely be met when a sponsor submits a waiver request in accordance with § 312.10(a) for the following reasons: (1) an alternate data lock point would permit the sponsor to coordinate the timing of submission of an annual FDA DSUR with the sponsor's submission of the proposed annual FDA DSUR to other INDs covered by the same annual FDA DSUR (*e.g.,* INDs for studies investigating other indications for a drug), (2) an alternate data lock point would permit the sponsor to coordinate the timing of submission of an annual FDA DSUR with the timing of submission of other reports to regulatory agencies in other countries and regions (*e.g.,* to coordinate the timing of submission of an annual FDA DSUR with the date of first approval or authorization for conducting a clinical investigation in any country or region (*i.e.,* the development international birth date of the drug)), or (3) an alternate data lock point would permit the sponsor to coordinate the timing of submission of an annual FDA DSUR with the timing of submission of the postmarketing periodic safety report required under 21 CFR 314.80(c)(2) or 600.80(c)(2), if a sponsor is submitting both reports to FDA (*e.g.,* is conducting clinical investigations of a lawfully marketed drug or biological product).

FDA expects that the waiver criteria in § 312.10(b) will probably be met when a sponsor submits a waiver request in accordance with § 312.10(a) to allow a sponsor to submit individual annual FDA DSURs for INDs that cover very different dosage forms of a drug (*e.g.,* the same active ingredient for intravenous use for a life-threatening disease versus topical administration for a more chronic disease) on the basis that submission of the same annual FDA DSUR for each IND would not be useful to FDA because of substantial differences in, for example, the intended uses or populations being studied.

3. Major Differences Between the Current IND Annual Report and the Proposed FDA DSUR

Table 1 shows the major differences between the current IND annual report and the proposed annual FDA DSUR.

TABLE 1—EXAMPLES OF MAJOR DIFFERENCES BETWEEN THE CURRENT REGULATORY REQUIREMENTS FOR THE IND ANNUAL REPORT AND THE REGULATORY REQUIREMENTS FOR THE PROPOSED FDA DSUR [1]

§ 312.33	Current IND annual report requirements	Proposed FDA DSUR requirements
Overall safety assessment	• Not required	• Requires providing a concise, integrated evaluation of all new clinical, nonclinical, and epidemiological safety information obtained about the drug by the sponsor during the reporting period in relation to the safety information obtained during prior reporting periods (proposed § 312.33(s)(1)) and a description of the balance between theoretical or anticipated benefits and cumulative identified risks related to use of the drug. • Requires a description of changes in the benefit-risk profile compared to the previous DSUR, based on information obtained during the reporting period (proposed § 312.33(s)(2))
Executive summary	• Not required	• Requires an executive summary (proposed § 312.33(c))
Scope of information on clinical investigations.	• Requires information about clinical investigations of the investigational drug under the IND (§ 312.33).	• Expands the scope to require comprehensive information about clinical investigations conducted anywhere in the world on behalf of the sponsor evaluating the drug or, including clinical investigations not conducted under an IND (proposed § 312.33(a)(1)).
Cumulative exposure	• Not required	• Adds the requirement to include the cumulative number of subjects exposed to the investigational drug and comparators during clinical investigations conducted on behalf of the sponsor and to include a tabulation of such exposure by age, sex, and race (proposed § 312.33(j)). • If the drug is lawfully marketed by the sponsor, the report must include an estimate of patients' cumulative exposure in any country or region, including an explanation of how that exposure was estimated (proposed § 312.33(j)).
Study description (individual study information).	• Requires a brief summary of the status of each study in progress and each study completed during the previous year, including the title of each study, its purpose, a brief statement identifying the patient population, and a statement as to whether the study is completed (§ 312.33(a)(1)).	• Requires an inventory of ongoing and completed clinical investigations conducted during the reporting period. • For each investigation in this inventory, requires the protocol number, the title, the clinical trial phase, the date the first subject provided informed consent, a brief description of clinical investigation design, and a brief description of the dose and regimen of the investigational drug and any comparators (proposed § 312.33(i)).

TABLE 1—EXAMPLES OF MAJOR DIFFERENCES BETWEEN THE CURRENT REGULATORY REQUIREMENTS FOR THE IND ANNUAL REPORT AND THE REGULATORY REQUIREMENTS FOR THE PROPOSED FDA DSUR [1]—Continued

§ 312.33	Current IND annual report requirements	Proposed FDA DSUR requirements
Study subjects (individual study information).	• Requires a brief summary of the status of each study in progress and each study completed during the previous year, including the following: —the total number of subjects initially planned for inclusion in the study (§ 312.33(a)(2)). —the number of subjects entered into the study to date (tabulated by age group, sex, and race). —the number whose participation in the study was completed as planned, and —the number who withdrew from the study for any reason (§ 312.33(a)(2)).	• Requires an inventory of ongoing and completed clinical investigations conducted during the reporting period. • For each investigation in this inventory, requires the cumulative number of subjects enrolled in all treatment arms of the investigation (or an estimate); a demographic breakdown of study population by age, sex, and race; and the total number of subjects (if any) planned to be enrolled in the clinical investigation (proposed § 312.33(i)). • Requires a list of subjects who withdrew from a clinical investigation during the reporting period because of an adverse event (proposed § 312.33(k)(1)(iv) and § 312.33(s)(iv)).
Study results (individual study information).	• In a brief summary of the status of each study in progress and each study completed during the previous year, requires including a brief description of any available study results if a study has been completed or if interim results are known (§ 312.33(a)(3)).	• Requires a brief summary of safety and effectiveness findings obtained from clinical investigations conducted on behalf of the sponsor of the investigational drug during the reporting period, including results obtained from any completed trials or interim analysis that resulted in a decision, based on lack of efficacy, to either stop a trial or to revise the information provided to subjects to seek informed consent (proposed § 312.33(*l*)).
Safety findings from other sources.	• Not required	• Adds the requirement that a sponsor submit a brief summary of relevant safety findings from other sources, if known, including noninterventional studies of the drug; pooled or meta-analyses of randomized clinical investigations of the drug; safety findings from marketing experience, if the drug is lawfully marketed; nonclinical studies of the drug; published clinical or nonclinical investigations of the drug not conducted on behalf of the sponsor; and published studies concerning other members of the pharmacological class of the drug. • The brief summary would also include all additional significant safety findings about the drug that are obtained from other sources during the reporting period, if known, including expanded access use under part 312, subpart I, or a similar program conducted on behalf of the sponsor in another country or region (proposed § 312.33(m)).
Serious adverse experiences.	• Requires a narrative or tabular summary showing the most frequent and most serious adverse experiences by body system (§ 312.33(b)(1)).	• Requires a list of all serious suspected adverse reactions as defined in § 312.32(a) that occurred during the reporting period, including the treatment group assignment, if known, or designated as ''blinded'' if the blind has not been broken. • Requires that the line listings identify serious and unexpected suspected adverse reactions as defined in § 312.32(a) and that they also include study identification information as listed (proposed § 312.33(k)(1)(i)). • Requires a summary list of serious adverse events for all clinical investigations conducted on behalf of the sponsor that occurred since the date the IND went into effect (proposed § 312.33(k)(1)(ii)).
IND safety reports	• Requires a summary of all IND safety reports submitted during the past year (§ 312.33(b)(2)).	
Information on drug's actions.	• Requires a brief description of what information, if any, was obtained during the previous year's clinical and nonclinical investigations that is pertinent to an understanding of the drug's actions (such as dose response, bioavailability) (§ 312.33(b)(5)).	• A brief description is not required for this section because information that is more detailed is required elsewhere in the proposed rule.
Nonclinical studies and findings.	• Requires a list of preclinical studies (including animal studies) completed or in progress during the past year and a summary of the major preclinical findings (§ 312.33(b)(6)).	• Changes the requirement to focus on safety by requiring a summary of safety findings from other sources for the reporting period, including nonclinical in vivo and in vitro studies; published nonclinical studies not conducted on behalf of the sponsor; and published studies on other members of the pharmacological class of the drug (proposed § 312.33(m)).
Manufacturing and microbiological changes.	• Requires a summary of any significant manufacturing or microbiological changes made during the past year (§ 312.33(b)(7)).	• Revises the current requirement so that sponsors would be required to provide a summary of significant chemistry, manufacturing, and control changes, including microbiological changes (if applicable), made to the investigational drug during the reporting period. • Requires a brief description of the safety significance of the identified changes (proposed § 312.33(n)).
Investigator brochure changes.	• If the investigator brochure has been revised, requires a description of the revision and a copy of the new brochure (§ 312.33(d)).	• States that, if the sponsor must submit an investigator brochure under § 312.23(a)(5), the brochure will serve as the reference safety information during that reporting period. • If an investigator brochure is not required under § 312.23(a)(5) and the drug is subject to an FDA-approved marketing application, the FDA-approved prescribing information will serve as the reference safety information during the reporting period. • If neither is the case and the sponsor uses another source as the reference safety information, the report must identify the reference safety information used (e.g., coding dictionary version(s) used). • Requires that the report list all safety-related changes to the reference safety information made during the reporting period.
Actions taken for safety reasons.	• Requires a brief summary of significant foreign marketing developments with the drug during the past year, such as approval of marketing in any country or withdrawal or suspension from marketing in any country (§ 312.33(f)).	• Requires a description of all actions relevant to safety and reasons for such actions taken during the reporting period by the sponsor (including actions taken following a recommendation from a DMC) or by a regulatory authority.

TABLE 1—EXAMPLES OF MAJOR DIFFERENCES BETWEEN THE CURRENT REGULATORY REQUIREMENTS FOR THE IND ANNUAL REPORT AND THE REGULATORY REQUIREMENTS FOR THE PROPOSED FDA DSUR [1]—Continued

§ 312.33	Current IND annual report requirements	Proposed FDA DSUR requirements
Event otherwise omitted from safety tabulations because it is a study endpoint.	• Not required	• Requires identifying each event omitted from the listings and tabulations of safety data required by § 312.33(k)(1) because the event is a study endpoint or a component of a study endpoint (proposed § 312.33(k)(2)).
Summary of important risks.	• Not required	• Requires providing a cumulative listing and a brief description of all important known and potential risks associated with the drug identified by the sponsor during the course of studies of the drug conducted on behalf of the sponsor. • Requires an update of the risks identified in a prior reporting period with any new risk information obtained during the current reporting period (proposed § 312.33(t)).
Exceptions for sponsor-investigators.	• Provides no distinction between sponsor-investigators and other sponsors (§ 312.33).	• States that a sponsor-investigator for a clinical investigation not intended to support a marketing application is required to submit only information obtained from the clinical investigation conducted by the sponsor-investigator (proposed § 312.33(a)(2)).
Conclusion	• Not required	• Requires including a conclusion (proposed § 312.33(u)).

[1] This table compares the regulatory requirements in current § 312.33 with the new requirements in proposed § 312.33. Although current annual reporting practices may go further than that required by the current regulations to be more consistent with the E2F DSUR, this table only highlights the regulatory requirements and not common practices.

4. FDA DSUR Content

FDA acknowledges that the proposed content requirements of the annual FDA DSUR are more extensive than generally would be needed for reporting the status of a sponsor-investigator IND for a single clinical investigation that is not intended to support a marketing application. Therefore, we are proposing that the report for an IND conducted by a *sponsor-investigator* (as defined in § 312.3) that is not intended to support a marketing application must contain the required information that is obtained from the investigation conducted by the sponsor-investigator (see § 312.33(a)(2)). The sponsor-investigator is required to submit only information that is obtained from the clinical investigation conducted by the sponsor-investigator (*e.g.,* information that is part of that sponsor-investigator's protocol for the IND). For example, if a commercial IND sponsor provides an investigational drug to a sponsor-investigator to conduct an investigation under the sponsor-investigator's IND, it would not be necessary for the sponsor-investigator to submit information unrelated to their study (*e.g.,* data concerning animal toxicity, drug manufacturing information, or safety information from investigations conducted under the commercial sponsor's IND) because the information would be submitted by the sponsor. Also, the sponsor-investigator may not have right of reference to the data. For these reasons, we do not propose requiring the sponsor-investigator to provide information in the annual FDA DSUR that is not obtained from the sponsor-investigator's own clinical investigation under an IND.

Proposed § 312.33(a)(3) provides that, in § 312.33, ongoing clinical investigations consist of all active investigations, including those that are on clinical hold; investigations that have not been terminated; and investigations for which a final study report has not been submitted but the investigation might otherwise be completed. The intent is to capture all relevant investigations conducted on behalf of the sponsor.

Proposed § 312.33(b) through (u) describe the content FDA proposes to be included in the annual FDA DSUR.

Proposed § 312.33(b) describes the content of the title page, including the IND number, report number (reports to be numbered sequentially), name of the investigational drug, reporting period, date of the report, and sponsor's name and address. The reporting period is the designated 12-month period during which information was obtained for the annual FDA DSUR and ending with the data lock point. This period would run from the previous anniversary of the date the IND went into effect under § 312.40(b) until 1 calendar day before the anniversary of the date the IND went into effect unless FDA grants a waiver pursuant to § 312.10(b) for the sponsor to designate an alternate date for the data lock point.

Proposed § 312.33(c) describes the content of the executive summary for the proposed annual FDA DSUR. Proposed § 312.33(c) would require that the executive summary contain all of the following information:

- The report number and reporting period;
- A brief description of the investigational drug, including the therapeutic class(es), pharmacological class (if applicable), and mechanism of action (if known), and the indications, doses, formulations, and routes of administration being studied on behalf of the sponsor;
- The cumulative number of subjects to whom the drug has been administered throughout the course of studies of the drug conducted on behalf of the sponsor or an estimate of these subjects if a precise number cannot be determined (*e.g.,* for a study that is currently enrolling subjects);
- A summary of the overall safety assessment required under proposed § 312.33(s) of the main report;
- A summary of the list of important risks required under proposed § 312.33(t) of the main report;
- A summary of actions taken for safety reasons as required under proposed § 312.33(g);
- A list of countries and regions (if a drug product is approved by a region, which may be the case in the EU) in which the drug has been approved for marketing; and
- A summary of the conclusion as required under proposed § 312.33(u) of the main report.

We are proposing to require that the report contain a table of contents with sufficient detail to direct the annual FDA DSUR reader to each of the components of the report described in paragraphs (e) through (u) of proposed § 312.33 (see proposed § 312.33(d)).

We are proposing to require a detailed introduction containing the following information: (1) identification of the reporting period; (2) a brief description of the investigational drug (including the therapeutic class(es), pharmacological class (if applicable), and the mechanism of action (if known); (3) a list of the indications, doses, formulations, and routes of administration being investigated; and (4) a list of the clinical investigations conducted on behalf of the sponsor that are referred to in the report (see § 312.33(e)).

Section 312.33(e) in this proposed rule corresponds to section 3.1 (Introduction) of the E2F DSUR. In comparing these sections, we note that section 3.1 of the E2F DSUR recommends the inclusion of certain information that is not included in FDA's proposed § 312.33(e), such as information about the Development International Birth Date; a short summary of the scope of the clinical trials covered by the report; and a brief description and explanation of all information that has not been included in the annual FDA DSUR. FDA is not requiring this information under proposed § 312.33(e) because the information is not expected to provide additional important information for FDA's safety evaluation of the drug.

Proposed § 312.33(e) would require information about the drug's therapeutic class(es) and pharmacological class (with pharmacological class included as part of the original IND per § 312.23(a)(3)) because therapeutic class is important to FDA's evaluation of drugs and biologics, and pharmacological class is important to FDA's evaluation of drugs. Also, proposed § 312.33(e) would require that the mechanism of action rather than the mode of action (the term used in the E2F DSUR) be included in the description of the drug because other FDA IND regulations already use the term mechanism of action (see, *e.g.,* § 312.23(a)(8)(i)). Unlike the E2F DSUR recommendations, FDA does not propose to require in this section information about population or populations being studied because FDA would receive this information pursuant to proposed § 312.33(i). Lastly, FDA does not propose to require in this section a rationale for the submission of multiple annual FDA DSURs for the investigational drug because FDA proposes to require sponsors to prepare and submit a single report for a drug studied under multiple INDs. If a sponsor is unable to comply with this requirement (*e.g.,* the sponsor would like to submit separate annual FDA DSURs for individual INDs), the sponsor may submit a waiver request in accordance with § 312.10(a) that includes information that justifies a waiver.

We are proposing that if the drug has been approved anywhere in the world, the sponsor would be required to provide a brief summary of the status of the approved drug, including the date of first approval, the indication(s), the approved dose(s), and where approved, (see proposed § 312.33(f)). This proposed requirement is consistent with the content recommended in section 3.2 (Worldwide Marketing Approval Status) of the E2F DSUR.

We are proposing to require that the sponsor describe all actions relevant to the safety of the drug that were taken by the sponsor or by a regulatory authority during the reporting period, if known (see proposed § 312.33(g)). The sponsor's actions include any actions taken by the sponsor in response to a regulatory action or any actions taken by the sponsor following a recommendation from a Data Monitoring Committee (DMC), if one is used. Proposed § 312.33(g) would also require the sponsor to provide the reason or reasons for each action.

The corresponding section 3.3 (Actions Taken in the Reporting Period for Safety Reasons) of the E2F DSUR recommends, in addition, actions related to safety that have been taken by an ethics committee. While some countries use established ethics committees with responsibilities that differ from those of institutional review boards in the United States, FDA believes that actions taken by an ethics committee in another country would often be included in a report of actions taken by sponsors or regulatory authorities. Section 3.3 of the E2F DSUR includes a list of examples of significant actions taken for safety reasons, which is similar in concept to the list of actions in proposed § 312.33(g). As such, FDA considers the information recommended in section 3.3 of the E2F DSUR to be substantially similar to what is called for by proposed § 312.33(g). The intent of proposed § 312.33(g) is to capture actions taken for safety reasons by the sponsor and by FDA in the United States and to capture analogous actions taken by regulatory authorities in other countries or regions. The intent is also to capture only actions that are significant to the conduct of clinical investigations under the IND, including the following examples of the types of actions to be reported under the proposed requirements:

- A clinical hold order issued under § 312.42;
- Denial of authorization to initiate a clinical investigation or the suspension of the conduct of a clinical investigation involving use of the drug in another country or region (*e.g.,* this includes early termination of an ongoing clinical trial because of safety findings or lack of efficacy);
- A requirement to cease distribution of the drug or other action related to the quality of the drug (*e.g.,* recall of the drug);
- Refusal to approve any application for marketing of the drug (this includes voluntary withdrawal of an application);
- An action by a regulatory authority that places a condition or limitation on the use or development of the drug (*e.g.,* a requirement to conduct long-term animal testing before beginning long-term studies in humans, the need for a validated immunogenicity assay before beginning phase 3 testing, specific testing needed before initiating pediatric studies, the limitation on dosing pending additional safety data, the exclusion of a particular population from clinical investigations);
- A safety-related change in the protocol or in the investigational plan of an ongoing clinical investigation of the drug (*e.g.,* change in dose, change in inclusion/exclusion criteria, monitoring that is new or more intensive, limit to the duration of the trial);
- A safety-related change in the information provided to human subjects in order to obtain informed consent for a clinical investigation of the drug;
- A safety-related formulation change to the drug;
- A safety advisory communication to investigators conducting studies under the IND or to healthcare professionals concerning use of the drug;
- An investigation of the drug that is initiated or planned to evaluate a safety risk associated with use of the drug;
- If the drug is lawfully marketed, each safety-related change to its labeling, including the prescribing information;
- If the drug is lawfully marketed, a significant restriction on distribution or other risk mitigation strategy (*e.g.,* a risk evaluation and mitigation strategy implemented under section 505–1 of the FD&C Act (21 U.S.C. 355–1)); and
- If the drug was lawfully marketed, withdrawal or suspension of marketing approval for the drug in any country or region.

We are proposing that the investigator brochure, if required under §§ 312.23(a)(5) and 312.55, will serve as the reference safety information to be used during the clinical investigation of the investigational drug. The investigator brochure in effect at the start of the reporting period will represent the reference safety information to be used by the sponsor during that reporting period. If an investigator brochure is not required and the drug is subject to an FDA-approved marketing application, we propose that the FDA-approved prescribing information will serve as the reference safety information. If an investigator brochure is not required under §§ 312.23(a)(5) and 312.55, the drug is not FDA-approved; and if the sponsor uses another source as the reference safety information, the

sponsor would be required to identify the reference safety information (*e.g.,* coding dictionary version(s) used or the European Summary of Product Characteristics) (see proposed § 312.33(h)(1)).

We are also proposing to require the sponsor to provide a report that lists all safety-related changes to the reference safety information, if applicable, during the reporting period. If the investigator brochure is used as the reference safety information, changes to that information would include revisions made to the investigator brochure by the sponsor as described in § 312.55(b) (see proposed § 312.33(h)(2)).

We are proposing to require the sponsor to provide an inventory of ongoing and completed clinical investigations of the investigational drug that were conducted on behalf of the sponsor during the reporting period (see proposed § 312.33(i)). The intent is to identify the universe of clinical investigations that are conducted under the IND. For each clinical investigation identified, the sponsor would be required to provide the following information:

- The protocol number.
- The clinical investigation title (or abbreviated title).
- The National Clinical Trial (NCT) number, if applicable.
- The phase of the clinical investigation (*i.e.,* 1, 2, 3, or postmarketing).
- The date the first subject provided informed consent.
- A brief description of the clinical investigation design and the dose and regimen of the investigational drug and any comparators.
- The cumulative number (or an estimate) of subjects enrolled in each treatment arm for all treatment arms of the clinical investigation during the reporting period.
- Countries or regions in which the clinical investigation was conducted. This would include any country or region with one or more study sites.
- A demographic breakdown of study population by age, sex, and race.
- The status of the clinical investigation (ongoing or completed).
- The total number of subjects (if any) planned to be enrolled in the clinical investigation.

We are proposing that the report identify the cumulative number of subjects exposed to the investigational drug and comparators (placebo and active controls) since the date the IND went into effect (see proposed § 312.33(j)(1)). For blinded studies, this number would be estimated. It would also require that such exposure be broken down by age, sex, and race. Proposed § 312.33(j)(2) would further require the report to estimate patients' cumulative exposure to the marketed drug in each country and region in which the sponsor has lawfully marketed the drug since the date the IND went into effect, if any, accompanied by an explanation of how that exposure was estimated. The estimate of exposure is intended to provide context (*i.e.,* a denominator) for the cumulative summary tabulations of serious adverse events and the overall assessment of safety.

Proposed § 312.33(k)(1) generally would require lists of safety data and other information from clinical investigations of the investigational drug conducted on behalf of the sponsor. Proposed § 312.33(k)(1) would not require information about adverse events that are study endpoints or components of study endpoints (*e.g.,* mortality events in an outcomes trial).

Proposed § 312.33(k)(1)(i) would require line listings of serious suspected adverse reactions as defined in § 312.32(a) that occurred during the reporting period, including the treatment associated with the serious suspected adverse reaction, as well as all serious suspected adverse reactions for any comparators, if known. The line listing would identify those serious suspected adverse reactions that are unexpected (*serious and unexpected suspected adverse reactions*), as defined in § 312.32(a). The line listing should be formatted as a detailed record of the serious suspected adverse reactions and would also be required to include the following information, if applicable:

- Study title or abbreviated title.
- Subject's clinical trial identification number.
- Sponsor's adverse reaction case reference number.
- IND Safety Report reference number.
- Country in which case occurred.
- Age and sex of trial subject.
- Treatment group; identified as ''blinded'' if the blind has not been broken.
- Dose and dosing interval of investigational drug and, when relevant, dosage form and route of administration.
- Date of onset and/or time to onset from administration of last dose of the most serious suspected adverse reaction.
- Dates of treatment and/or best estimate of treatment duration of serious suspected adverse reaction.
- Outcome (*e.g.,* resolved, fatal, improved, sequelae, unknown). This field must indicate the consequences of the reaction(s) for the trial subject, using the worst of the different outcomes for multiple reactions.
- Comments (*e.g.,* causality assessment if the sponsor disagrees with the reporter; concomitant medications suspected to play a role in the reactions directly or by interaction; indication treated with suspect drug(s); dechallenge/rechallenge results if available).

The study identification information included with the line listing of serious suspected adverse reactions required under proposed § 312.33(k)(1)(i) would facilitate FDA's evaluation of the drug's safety information across multiple clinical trials and INDs.

Proposed § 312.33(k)(1)(ii) would require a cumulative summary tabulation *of serious adverse events* as defined in § 312.32(a) for all clinical investigations conducted on behalf of the sponsor since the date the IND went into effect under § 312.40(b). This summary should be formatted as a table.

Proposed § 312.33(k)(1)(iii) would require a list of study subjects who died during the reporting period and the cause of death.

Proposed § 312.33(k)(1)(iv) would require a list of subjects who withdrew from a clinical investigation during the reporting period because of an adverse event as defined in § 312.32(a), whether the adverse event was related to the investigational drug or not.

The line listings and cumulative summary lists required under proposed § 312.33(k)(1) correspond to section 3.7 (Data in Line Listings and Summary Tabulations) of the E2F DSUR, which includes slightly different information as a result of differences in terminology in safety reporting standards. Specifically, FDA issued a final ICH guidance for industry in March 1995 entitled ''E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting'' (ICH E2A Clinical Safety Data Management guideline) (available at *https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073087.pdf*). The E2F DSUR cross-referenced definitions for serious adverse reaction, serious adverse event, and adverse drug reaction as defined in the ICH E2A Clinical Safety Data Management guideline. The ICH Clinical Safety Data Management guideline defines adverse drug reaction as ''All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase 'responses to medicinal products' means that a causal relationship between a medicinal product and an adverse event is at least

a reasonable possibility, *i.e.,* the relationship cannot be ruled out.'' However, FDA issued a final rule entitled ''Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans'' on September 29, 2010 (75 FR 59935), which revised the definitions of these safety reporting terms under current § 312.32(a). As a result, instead of using the term *adverse drug reaction* as defined in the ICH E2A Clinical Safety Data Management guideline, we are using *suspected adverse reaction,* which is defined under current § 312.32(a). For the purposes of IND safety reporting, ''reasonable possibility,'' as it appears in § 312.32(a), 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. We are also making use of the term *serious adverse event* or *serious suspected adverse reaction* as defined in § 312.32(a). In light of this revision in terminology, we are making it clear that sponsors would be required under proposed § 312.33(k)(1)(i) to provide a line listing of all serious suspected adverse reactions. We note that adverse reactions, which are defined under current § 312.32(a) as adverse events caused by a drug, are a subset of all suspected adverse reactions—for which there is reason to conclude that the drug caused the event—and, if serious, would be required to be included in the line listings for proposed § 312.33(k)(1)(i).

FDA's requirements under proposed § 312.33(k)(1) for a list of study subjects who died during the reporting period and the cause of death and for a list of subjects who withdrew from the clinical investigation during the reporting period correspond to section 3.16 (Region-Specific Information) of the E2F DSUR, which similarly includes a list of subjects who died during the reporting period, the case number, the assigned treatment, and the cause of death for each subject, as well as a list of subjects who withdrew from clinical investigations during the reporting period in association with an adverse event. The E2F DSUR states that information should include whether or not withdrawing from the investigation was thought to be drug-related.

We are further proposing that a sponsor identify each event omitted from these listings or tabulations because the event is a study endpoint or a component of a study endpoint (see proposed § 312.33(k)(2)). This provision is intended to account for study endpoints in outcome studies in which death or major morbidity is the study endpoint (an adverse outcome) and to isolate those events from other reported adverse events. For example, deaths in a cancer trial in which overall survival is the study endpoint would be identified as required in proposed § 312.33(k)(2) and omitted from the safety line listings and summary tabulations described in proposed § 312.33(k)(1). Similarly, fatal strokes that are a component of a composite primary study endpoint (*e.g.,* all-cause mortality) would be identified as required by proposed § 312.33(k)(2) and omitted from the listings and summary tabulations of serious adverse events described in proposed § 312.33(k)(1).

We are proposing that the report briefly summarize all safety and effectiveness findings from clinical investigations of the investigational drug conducted on behalf of the sponsor that are obtained during the reporting period (see proposed § 312.33(*l*)). Statistically significant differences would be an example of such a finding, but in addition, clinically meaningful differences identified in an interim analysis that were provided to the sponsor and that led to a change in the protocol or population would also be required. The report would include data from any completed trials, interim analyses of ongoing trials, or long-term follow-up of subjects after exposure to the investigational drug in a clinical trial (*e.g.,* for advanced therapies such as gene therapy, cell therapy, or tissue-engineered products). In certain cases, the lack of effectiveness on an endpoint compared to a comparator (*e.g.,* cardiovascular events) can be a safety issue. Therefore, it is important to also report on studies in which there was a lack of effectiveness or lesser effectiveness relative to an active comparator, including results obtained from any completed trials or interim analysis that influenced a decision, based on lack of efficacy, to either stop a trial or to revise the documents provided to subjects when seeking informed consent.

Proposed § 312.33(m) is intended to ensure that all information that is relevant to the safety of the drug and obtained during the reporting period from any source is considered and analyzed in the report. This proposed section would require the report to briefly summarize the following safety information, if known:

- Noninterventional studies where participants are not prospectively assigned to receive a drug or other intervention per a protocol, including observational studies, epidemiological studies, registries, and active surveillance.
- Pooled or meta-analyses of randomized clinical investigations.
- Safety findings from marketing experience, if the drug is lawfully marketed in any country or region.
- Nonclinical in vivo and in vitro studies (*e.g.,* carcinogenicity, reproductive toxicity, immunotoxicity studies).
- Published clinical or nonclinical investigations of the drug not conducted on behalf of the sponsor.
- Published studies of other members of the drug's pharmacological class. Section 3.13 (Literature) of the E2F DSUR provides for the inclusion of information from unpublished studies of which the sponsor has become aware during the reporting period. This section of the proposed rule would require information from published studies and does not create a requirement for sponsors to seek out unpublished studies that may be related to the drug.
- All additional significant safety findings about the drug from other sources. In addition, safety information provided by codevelopment partners or safety information from investigator-initiated trials would also be captured under this bullet and is consistent with section 3.10 (Other Clinical Trial/Study Safety Information) of the E2F DSUR.

We are proposing that the report include a summary of all significant chemistry, manufacturing, and control changes, including microbiological changes (if applicable), made to the investigational drug during the reporting period and briefly describe the safety significance of the identified changes (see proposed § 312.33(n)).

We are proposing that the report briefly describe each significant modification made to protocols in response to safety data on behalf of the sponsor for clinical investigations being conducted with the investigational drug that were not previously reported under § 312.30 (see proposed § 312.33(o)). The intent of this proposed regulation is to provide awareness of significant modifications related to safety issues in trials being conducted in another country or region and not under an IND.

We are proposing that the report contain a description of the general investigational plan for the coming year to replace the plan submitted 1 year earlier (consistent with the content of the general investigational plan described in § 312.23(a)(3)(iv)) (see proposed § 312.33(p)).

We are providing the sponsor the option of including a log of any outstanding business concerning the IND for which the sponsor requests a reply, comment, or meeting (see proposed § 312.33(q)).

We are proposing that the report describe any potentially important late-breaking safety information about the investigational drug or the studies conducted under the IND that were identified by the sponsor during preparation of the annual FDA DSUR and after the data lock point (see proposed § 312.33(r)). The types of findings or actions that would be required to be described under proposed § 312.33(r) include clinically significant new adverse event reports; important follow-up data; clinically relevant toxicological findings; and actions taken for safety reasons that, if the actions had occurred before the data lock point, would have been described as required under proposed § 312.33(g). This proposed section is intended to capture findings that would have been included in the body of the report but did not come to the sponsor's awareness until after the data lock point when the sponsor was preparing the annual FDA DSUR.

We are proposing that the report provide an overall safety assessment that is a concise, integrated evaluation of all new clinical, nonclinical, and epidemiological safety information obtained by the sponsor during the reporting period relative to previous knowledge of the drug (see proposed § 312.33(s)(1)). Proposed § 312.33(s)(1) is not intended to require a repeat of information or a summary of information presented in previous sections of the annual FDA DSUR; rather, it would require an interpretation of the information and its implications for the IND. This proposed section corresponds to section 3.18.1 (Evaluation of the Risks) of the E2F DSUR, and both provide relevant points to consider (if applicable) for evaluating the risks of the drug. The integrated evaluation required under proposed § 312.33(s)(1) would include the following: (1) cumulative experience with the drug, (2) new information about the drug that was collected during the reporting period covered by the proposed annual FDA DSUR, and (3) for drugs with a marketing approval, clinically significant postmarketing data related to the drug. This proposed section of the report would explain how safety information obtained during the reporting period integrates with what was already known about the drug (*e.g.,* what was in prior annual FDA DSURs). The assessment must include an evaluation of the following information potentially relevant to the risk associated with use of the drug:

- Findings that suggest a significant risk in humans exposed to the drug, with associated laboratory values and relationship to dose, duration, or time course of exposure, if known.
- Significant changes to the information concerning an adverse event that was contained in a previous report (*e.g.,* increased frequency, increased severity, identification of a population at greater risk for this adverse event).
- Deaths that were previously included in an IND safety report required under § 312.32.
- Subject withdrawals from a clinical investigation resulting from an adverse event.
- Findings that suggest a significant risk to specific populations (*e.g.,* pediatric, geriatric, populations with hepatic or renal impairment, pregnant or lactating women, populations differentiated by genomic or genetic characteristics).
- Overdose, misuse, and abuse cases or findings regarding the potential for abuse to occur.
- Risks associated with long-term exposure (*e.g.,* a drug used to treat a chronic disease).
- Risks associated with the method of administration of the drug (*e.g.,* drugs administered by injection or drugs administered by intravenous, intrathecal, or inhalation methods might be associated with the risk of increased local concentrations, sterility, pyrogenicity, hypersensitivity, or variations in metabolism), diagnostic procedures related to use of the drug (*e.g.,* an invasive sampling procedure), or procedures described in a study protocol.
- Evidence of clinically significant medication errors (*i.e.,* any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of a healthcare provider, patient, or consumer).
- Drug interactions (*e.g.,* drug-drug, drug-food).
- Any other risks that significantly affect the safety assessment of the investigational drug.

We are proposing that the overall safety assessment also describe the balance between benefits, including theoretical or anticipated benefits, and cumulative identified risks related to use of the drug (see proposed § 312.33(s)(2)). The assessment would also be required to describe all changes to the benefit-risk profile compared to the previous annual report, based on information obtained during the reporting period. Proposed § 312.33(s)(2) is not intended to require a full benefit-risk assessment of the drug.

We are proposing that the report contain a cumulative listing of all important known risks (*i.e.,* risks established to be related to the use of the drug) and potential risks (*i.e.,* risks that have a reasonable possibility of a relationship to the drug, but have not yet been established) associated with the drug that are identified by the sponsor during the course of studies of the drug conducted on behalf of the sponsor, along with a brief description of the nature of each risk (see proposed § 312.33(t)). Such risks might include, for example, toxicities known to be associated with a particular molecular structure or drug class or concerns based on accumulating nonclinical or clinical data. Risks identified in a prior reporting period would be required to be re-evaluated annually and a description of each risk updated with new risk information obtained during the current reporting period. Risks that have been fully addressed or resolved would be required to remain in the summary and be briefly described (*e.g.,* findings from toxicology studies or early clinical trials that were not borne out by later clinical data).

Proposed § 312.33(t) would require a summary of all important known and potential risks, whereas proposed § 312.33(s) would provide an overall safety assessment.

We are proposing that the report include a conclusion to briefly summarize the following information: (1) all changes to the sponsor's previous knowledge of efficacy and safety of the investigational drug resulting from information obtained during the reporting period, (2) an outline of actions that the sponsor has taken during the reporting period to address emerging safety findings, and (3) all additional actions that the sponsor will take to address emerging safety findings in the future (see proposed § 312.33(u)).

VI. Proposed Effective and Compliance Dates

FDA proposes that any final rule based on this proposed rule become effective 30 days after the final rule publishes in the **Federal Register**. FDA is proposing that the compliance date for any final rule based on this proposed rule be 180 days after the date of publication of such final rule to give sponsors sufficient time to compile the additional information that the proposed rule would require, if finalized. We request comments

specifically regarding the proposed compliance date.

VII. Preliminary Economic Analysis of Impacts

A. Introduction

We have examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). Executive Orders 12866 and 13563 direct us to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The Office of Information and Regulatory Affairs has determined that this proposed rule is an economically significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the proposed requirements are unlikely to impose a substantial burden on the affected small entities, we propose to certify that the proposed rule will not have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to 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 $165 million, using the most current (2021) Implicit Price Deflator for the Gross Domestic Product. This proposed rule would not result in an expenditure in any year that meets or exceeds this amount.

B. Summary of Costs and Benefits

The proposed rule seeks to revise FDA's regulations for IND annual reporting. The proposed rule would modify the format and content of the IND annual report to be generally consistent with those of the annual DSUR standards devised by the ICH. The proposed harmonization would result in savings in labor costs for certain sponsors who may no longer have to prepare a different type of periodic safety report for submission to certain other countries or regions in which a drug might be studied. Moreover, FDA would receive safety data on investigational new drugs that is more comprehensive, which would enhance our ability to oversee the progress and safety of clinical investigations. The estimate of annualized benefits over 10 years ranges from $47.86 million to $117.99 million with a primary value of $86.46 million at a 7 percent discount rate and from $49.24 million to $121.01 million with a primary value of $88.79 million at a 3 percent discount rate. The primary estimate of the present value of benefits over 10 years is $607.29 million at a 7 percent discount rate and $757.38 million at a 3 percent discount rate.

Costs would arise from increased labor associated with preparing and submitting a periodic safety report that is more comprehensive to meet the proposed requirements. Costs to government would arise from increased FDA resources being used to review the more comprehensive report. The estimate of annualized costs over 10 years ranges from $40.43 million to $101.34 million at a 7 percent discount rate with a primary value of $61.11 million. Using a 3 percent discount rate, the annualized costs range from $40.89 million to $102.48 million with a primary value of $61.81 million. The primary estimate of the present value of costs over 10 years is $429.20 million at a 7 percent discount rate and $527.21 million at a 3 percent discount rate. The annualized estimates are presented in Table 2.

TABLE 2—SUMMARY OF BENEFITS AND COSTS IN MILLIONS OF 2020 DOLLARS OVER A 10-YEAR TIME HORIZON

Category	Primary estimate	Low estimate	High estimate	Units			Notes
				Year dollars	Discount rates (%)	Period covered (years)	
Benefits:							
Annualized Monetized $/year	$86.46	$47.86	$117.99	2020	7	10	Benefits are estimated in terms of cost savings.
	88.79	49.24	121.01	2020	3	10	
Annualized Quantified	.....	.....	.....	.....	7		
					3		
Qualitative							
Costs:							
Annualized Monetized $/year	61.11	40.43	101.34	2020	7	10	
	61.81	40.89	102.48	2020	3	10	
Annualized Quantified	.....	.....	.....	.....	7		
					3		
Qualitative							
Transfers:							
Federal Annualized Monetized $/year	.....	.....	.....	.....	7		
					3		
From/To	From:			To:			
Other Annualized Monetized $/year	.....	.....	.....	.....	7		
					3		
From/To	From:			To:			

Effects:

State, Local or Tribal Government: None.

Small Business: Annual costs per affected small entity represent a maximum of 0.61 percent of average shipments.

TABLE 2—SUMMARY OF BENEFITS AND COSTS IN MILLIONS OF 2020 DOLLARS OVER A 10-YEAR TIME HORIZON—Continued

Category	Primary estimate	Low estimate	High estimate	Units			Notes
				Year dollars	Discount rates (%)	Period covered (years)	
Wages: None. Growth: None.							

C. Summary of Regulatory Flexibility Analysis

We estimate that at least 77 percent of establishments in the pharmaceutical preparations industry and at least 69 percent of establishments in the biological products industry employ fewer than 1,250 employees and are therefore also classified as small businesses. Although a large number of small businesses will face costs under the proposed rule, the costs to these firms would be relatively small. The average annual cost per IND annual report as a percentage of average value of shipments for small entities is estimated to be between 0.00 percent and 0.61 percent. We therefore conclude that this proposed rule is unlikely to have a significant impact on a substantial number of small entities.

We have developed a comprehensive Preliminary Economic Analysis of Impacts that assesses the impacts of the proposed rule. The full preliminary analysis of economic impacts is available in the docket for this proposed rule (Ref. 8) and at *https://www.fda.gov/about-fda/reports/economic-impact-analyses-fda-regulations.*

VIII. Analysis of Environmental Impact

We have 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.

IX. Paperwork Reduction Act of 1995

This proposed rule contains information collection provisions that are subject to review by OMB under the PRA (44 U.S.C. 3501–3521). A description of these provisions is given in the *Description* section with an estimate of the annual reporting burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

FDA invites comments on these topics: (1) whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Investigational New Drug Application Annual Reporting.

Description: FDA is proposing to revise its requirements for annual reports submitted to INDs. FDA is proposing to replace the current annual reporting requirement with a new annual reporting requirement that is intended to be generally consistent with the format and content of submission of the annual DSUR devised by the ICH and described in the E2F DSUR. The proposed annual FDA DSUR would provide an annual report that is more comprehensive and informative than the IND annual report required under current § 312.33. The E2F DSUR can be used to satisfy similar annual reporting requirements in certain other countries and regions in which a drug is being studied. Therefore, the proposed implementation of an annual reporting requirement similar to the E2F DSUR in place of the IND annual report format and content is consistent with FDA's overarching goal of fostering international harmonization of regulatory requirements to the extent appropriate and feasible. With the increasing complexity of clinical studies, DSURs that are more comprehensive and informative are important tools to identify and reduce exposure of human subjects to unnecessary risks. The proposed annual FDA DSUR would also help ensure FDA's ongoing oversight of the evolving safety and efficacy profile of the drug throughout the drug development process. We anticipate an additional regulatory burden associated with preparing the proposed annual FDA DSUR. However, for sponsors that currently prepare and submit the IND annual report to FDA and the E2F DSUR to another regulatory authority in another country or region, FDA expects that the burden associated with preparing two periodic safety reports will be reduced because the sponsors might no longer have to prepare two different annual safety reports, because the annual FDA DSUR and the E2F DSUR would be generally consistent in content and format.

Description of Respondents: Sponsors of clinical investigations under an IND.

In tables 4 and 5, the estimated averages for the number of respondents and total annual responses were obtained from CDER and CBER reports and data management systems.

In the approved package for OMB control number 0910–0014, FDA estimated 360 burden hours to complete and submit an IND annual report. To complete and submit the annual FDA DSUR, FDA estimates that a sponsor would spend an additional 18 to 72 hours because of the more comprehensive information not currently required by the IND annual report. Thus, we estimate that sponsors will spend a total of 396 hours to comply with the proposed requirement. The estimated average burden hours per response was made by CDER and CBER individuals familiar with the burden associated with these reports and from estimates received from the pharmaceutical industry. For the total information collection burden for preparing and submitting an annual FDA DSUR, FDA estimates 4,590,432 hours (3,855,456 CDER hours + 734,976 CBER hours = 3,430,944). The estimated 4,590,432 total hours includes 4,173,120 total hours to submit an IND annual report and 417,312 additional total hours to provide the additional information required in the annual FDA DSUR.

TABLE 4—ESTIMATED ANNUAL REPORTING BURDEN FOR HUMAN DRUGS REGULATED BY CDER [1]

21 CFR section	Number of respondents	Number of responses per respondent	Total annual responses	Average burden per response	Total hours
§ 312.33	2,877	3.38	9,736	396	3,855,456

[1] There are no capital or operating and maintenance costs associated with this collection of information.
Note: The Total Annual Responses may not sum up as a result of rounding.

TABLE 5—ESTIMATED ANNUAL REPORTING BURDEN FOR HUMAN DRUGS REGULATED BY CBER [1]

21 CFR section	Number of respondents	Number of responses per respondent	Total annual responses	Average burden per response	Total hours
§ 312.33	745	2.49	1,856	396	734,976

[1] There are no capital or operating and maintenance costs associated with this collection of information.
Note: The Total Annual Responses may not sum up as a result of rounding.

This proposed rule also refers to previously approved collections of information found in FDA regulations. The collections of information in part 312 have been approved under OMB control number 0910–0014.

In compliance with the PRA (44 U.S.C. 3407(d)), the Agency has submitted the information collection provisions of this proposed rule to OMB for review. These information collection requirements will not be effective until FDA publishes a final rule, OMB approves the information collection requirements, and the rule goes into effect. FDA will announce OMB approval of these requirements in the **Federal Register**.

X. Federalism

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. We have determined that the proposed 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, we conclude that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

XI. Consultation and Coordination With Indian Tribal Governments

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13175. We have tentatively determined that the rule does not contain policies that would have a substantial direct effect on one or more Indian Tribes, on the relationship between the Federal Government and Indian Tribes, or on the distribution of power and responsibilities between the Federal Government and Indian Tribes. The Agency solicits comments from tribal officials on any potential impact on Indian Tribes from this proposed action.

XII. References

The following references marked with an asterisk (*) are on display at the Dockets Management Staff (see **ADDRESSES**) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at *https://www.regulations.gov*. References without asterisks are not on public display at *https://www.regulations.gov* because they have copyright restriction. Some may be available at the website address, if listed. References without asterisks are available for viewing only at the Dockets Management Staff. FDA has verified the website addresses as of the date this document publishes in the **Federal Register**, but websites are subject to change over time.

1. CIOMS, ''Development Safety Update Report (DSUR) Harmonizing the Format and Content for Periodic Safety Report During Clinical Trials: Report of CIOMS Working Group VII,'' ''Introduction and Overview, Rationale for the CIOMS VII Project,'' Chapter I.a, pp. 11 and 12, Geneva 27, Switzerland, 2006.
* 2. ICH, Harmonisation for Better Health, ''Vision: Mission,'' accessed August 22, 2016.
* 3. ICH, ''ICH Steering Committee, Minneapolis, MN, USA,'' June 2014 (available at *https://www.ich.org/pressrelease/ich-steering-committee-minneapolis-mn-usa-june-2014*), accessed January 7, 2020.
* 4. ICH, ''Final Concept Paper, E2F: Development Safety Update Report,'' 2006 (available at *https://database.ich.org/sites/default/files/E2F_Concept_Paper.pdf*), accessed January 7, 2020.
* 5. ICH, Harmonised Tripartite Guideline ''Development Safety Update Report, E2F, Finalised Guideline,'' August 2010 (*https://database.ich.org/sites/default/files/E2F_Guideline.pdf*), accessed January 7, 2020.
* 6. EU, ''Communication From the Commission—Detailed Guidance on the Collection, Verification and Presentation of Adverse Event/Reaction Reports Arising From Clinical Trials on Medicinal Products for Human Use ('CT–3'),'' 2011 (available at *https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2011:172:0001:0013:EN:PDF*), accessed October 22, 2022.
* 7. European Medicines Agency, ''ICH Topic E 2 C (R1) Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs,'' June 1997 (available at *https://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002780.pdf*), accessed December 30, 2019.
* 8. FDA, Preliminary Regulatory Impact Analysis; Initial Regulatory Flexibility Analysis; Unfunded Mandates Reform Act Analysis, ''Investigational New Drug Application Annual Reporting,'' 2019 (available at *https://www.fda.gov/about-fda/reports/economic-impact-analyses-fda-regulations*).

List of Subjects in 21 CFR Part 312

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

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 312 be amended as follows:

PART 312—INVESTIGATIONAL NEW DRUG APPLICATION

■ 1. The authority citation for 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. Amend § 312.3(b) by alphabetically adding a definition for *Data lock point* to read as follows:

§ 312.3 Definitions and interpretations.

* * * * *

(b) * * *

Data lock point means the cutoff date for data to be included in the development safety update report required under § 312.33. The data lock point is 1 calendar day before the anniversary of the date the IND went into effect under § 312.40(b).

* * * * *

■ 3. Revise § 312.33 to read as follows:

§ 312.33 Development safety update reports.

Not later than 60 calendar days after the data lock point, a sponsor must submit to FDA a development safety update report (DSUR) as described in paragraphs (a) through (u) of this section.

(a) *Scope.* The DSUR is intended to provide a thorough annual assessment of clinical investigations conducted and safety information collected during the reporting period that are related to an investigational new drug.

(1) A sponsor must submit an annual DSUR that contains the information required to be submitted under paragraphs (b) through (u) of this section for all ongoing or completed clinical investigations conducted anywhere in the world on behalf of the sponsor evaluating the drug, including clinical investigations not conducted under an investigational new drug application (IND), unless otherwise specified in this section. The sponsor must submit the same DSUR for each IND held by the sponsor for any dosage form of the drug.

(2) A sponsor-investigator for a clinical investigation not intended to support a marketing application must provide information required under this section that is obtained from the clinical investigation conducted by the sponsor-investigator, but the sponsor-investigator is not required to submit information that is not obtained from the clinical investigation conducted by the sponsor-investigator.

(3) For the purposes of this section, ongoing clinical investigations consist of active clinical investigations, clinical investigations that are on clinical hold under § 312.42, clinical investigations that have not been terminated, and clinical investigations for which a final study report has not been submitted but the clinical investigation might otherwise be completed.

(b) *Title page.* The title page of the DSUR must contain the IND number, DSUR number (numbered sequentially), name of the investigational drug, reporting period, date of the DSUR, and sponsor's name and address.

(c) *Executive summary.* The executive summary must contain all of the following information:

(1) The DSUR number and reporting period.

(2) A brief description of the investigational drug (including the therapeutic class, pharmacological class (if applicable), and mechanism of action (if known)) and the indication(s), dose(s), formulation(s), and route(s) of administration being studied.

(3) The cumulative number of subjects to whom the drug has been administered throughout the course of clinical investigations of the drug conducted on behalf of the sponsor or, if a precise number cannot be determined, an estimate.

(4) A summary of the overall safety assessment required in paragraph (s) of this section.

(5) A summary of the list of important risks required in paragraph (t) of this section.

(6) A summary of actions taken for safety reasons as required in paragraph (g) of this section.

(7) A list of countries and regions in which the drug has been approved for marketing.

(8) A summary of the conclusion required in paragraph (u) of this section.

(d) *Table of contents.* The DSUR must contain a table of contents that is sufficiently detailed to direct the reader to the components of the DSUR as described in paragraphs (e) through (u) of this section.

(e) *Introduction.* The introduction must:

(1) Identify the reporting period;

(2) Briefly describe the investigational drug, including the therapeutic class, pharmacological class (if applicable), and mechanism of action (if known);

(3) List the indication(s), dose(s), formulation(s), and route(s) of administration being investigated; and

(4) List the clinical investigation(s) conducted on behalf of the sponsor that are referred to in the DSUR.

(f) *Worldwide marketing authorizations and applications.* If the drug has been approved for marketing anywhere in the world, the DSUR must provide a brief summary of the status of the approved drug, including date of first approval, indication(s), dose(s), and countries or regions in which it is approved.

(g) *Actions taken for safety reasons.* The DSUR must describe all actions relevant to the safety of the drug that were taken during the reporting period by a regulatory authority or by the sponsor, if known. For each action taken, the reason(s) the action was taken must be provided, if known. Actions taken by the sponsor include those actions taken in response to a regulatory action and those actions taken following a recommendation from a data monitoring committee. Actions relevant to the safety of the drug include, but are not limited to, any of the following:

(1) A clinical hold order issued under § 312.42;

(2) Denial of authorization to initiate a clinical investigation, or the suspension of the conduct of a clinical investigation of the drug in another country or region;

(3) A requirement to cease distribution of the drug or other action related to the quality of the drug;

(4) Refusal to approve any application for marketing of the drug;

(5) An action that places a condition or limitation on the use or development of the drug;

(6) A safety-related change in the protocol or investigational plan of an ongoing clinical investigation of the drug;

(7) A safety-related change in the information provided to human subjects in order to obtain informed consent for a clinical investigation of the drug;

(8) A safety-related formulation change to the drug;

(9) A safety advisory communication to investigators conducting clinical investigations under the IND or to healthcare professionals concerning use of the drug;

(10) A clinical investigation of the drug that is initiated or planned to evaluate a risk associated with use of the drug;

(11) If the drug is lawfully marketed, a safety-related change to its labeling, including the prescribing information;

(12) If the drug is lawfully marketed, a significant restriction on distribution or other risk mitigation strategy, including a risk evaluation and mitigation strategy (REMS) required under section 505–1 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355–1); and

(13) If the drug was lawfully marketed in the past, withdrawal or suspension of marketing approval for the drug.

(h) *Reference safety information.* (1) If required under §§ 312.23(a)(5) and 312.55, the investigator brochure in effect at the start of a reporting period will serve as the reference safety information for that reporting period. If an investigator brochure is not required under §§ 312.23(a)(5) and 312.55 and

the drug is subject to an FDA-approved marketing application, the FDA-approved prescribing information will serve as the reference safety information during the reporting period. If an investigator brochure is not required under §§ 312.23(a)(5) and 312.55 and the drug is not subject to an FDA-approved marketing application, the sponsor must use another source as the reference safety information. The sponsor must identify the reference safety information used during the reporting period.

(2) The DSUR must list all safety-related changes to the reference safety information, made during the reporting period.

(i) *Inventory of clinical investigations conducted during the reporting period.* For each ongoing and completed clinical investigation of the investigational drug conducted on behalf of the sponsor during the reporting period, the DSUR must provide the following:

(1) The protocol number;

(2) The clinical investigation title (or abbreviated title);

(3) The NCT number, if applicable;

(4) The phase of the clinical investigation (*i.e.,* 1, 2, 3, or postmarketing);

(5) The date the first subject provided informed consent;

(6) A brief description of the clinical investigation design and the dose and regimen of the investigational drug and any comparators;

(7) The cumulative number (or an estimate) of subjects enrolled in each treatment arm for all treatment arms of the clinical investigation;

(8) Countries or regions in which the clinical investigation was conducted;

(9) A demographic breakdown of study population by age, sex, and race;

(10) The status of the clinical investigation (*i.e.,* ongoing or completed); and

(11) The number of subjects (if any) planned to be enrolled in the clinical investigation.

(j) *Cumulative exposure.* (1) The DSUR must provide the cumulative number (or an estimate) of subjects exposed to the investigational drug and comparators during clinical investigations conducted on behalf of the sponsor since the date the IND went into effect. The DSUR must provide a tabulation of exposed subjects by age, sex, and race.

(2) If the drug is lawfully marketed by the sponsor, the DSUR must provide an estimate of patients' cumulative exposure to the drug in each country and region in which the sponsor has marketed the drug since the date the IND went into effect, including an explanation of how that exposure was estimated.

(k) *Safety data tabulations and line listings.* (1) The DSUR must provide the following safety data from clinical investigations of the investigational drug that are conducted on behalf of the sponsor, with the exception of adverse events that are study endpoints or components of study endpoints:

(i) Line listings of all serious suspected adverse reactions as defined in § 312.32(a) that occurred during the reporting period, as well as all serious suspected adverse reactions for any comparators, if known. The line listings must identify those serious suspected adverse reactions that are unexpected (serious and unexpected suspected adverse reaction) as defined in § 312.32(a) and must also include the following information, if applicable:

(A) Clinical investigation identification information (*e.g.,* number or name).

(B) Subject's clinical investigation identification number.

(C) Sponsor's adverse reaction case reference number.

(D) IND Safety Report reference number.

(E) Country in which case occurred.

(F) Age and sex of subject.

(G) Treatment group; identified as ''blinded'' if the blind has not been broken.

(H) Dose and dosing interval of investigational drug and, when relevant, dosage form and route of administration.

(I) Date of onset and/or time to onset from administration of last dose of the most serious suspected adverse reaction.

(J) Date(s) of treatment and/or best estimate of treatment duration.

(K) The DSUR must indicate the consequences of the reaction(s) for the subject, using the worst of the different outcomes for multiple reactions.

(L) Comments.

(ii) A cumulative summary tabulation of serious adverse events (as defined in § 312.32(a)) obtained from all clinical investigations conducted on behalf of the sponsor that occurred since the date the IND went into effect under § 312.40(b).

(iii) A list of subjects who died during the reporting period and the cause of death for each subject.

(iv) A list of subjects who withdrew from a clinical investigation during the reporting period because of an adverse event (as defined in § 312.32(a)), whether the adverse event was related to the investigational drug or not.

(2) The DSUR must identify each event omitted from the information reported pursuant to paragraph (k)(1) of this section because the event is a study endpoint or a component of a study endpoint.

(l) *Results from clinical investigations.* The DSUR must briefly summarize all safety and effectiveness findings from clinical investigations of the investigational drug that are conducted on behalf of the sponsor and obtained during the reporting period, including results obtained from any completed clinical investigations or interim analysis that resulted in a decision, based on lack of efficacy, to either stop a clinical investigation or to revise the information provided to subjects when seeking to obtain informed consent.

(m) *Other safety findings.* The DSUR must briefly summarize the following information obtained during the reporting period, if known:

(1) Noninterventional studies of the drug, including observational studies; epidemiological studies; registries; and active surveillance.

(2) Pooled analyses or meta-analyses of randomized clinical investigations of the drug.

(3) Safety findings from marketing experience if the drug is lawfully marketed.

(4) Nonclinical in vivo and in vitro studies of the drug.

(5) Published clinical or nonclinical investigations of the drug not conducted on behalf of the sponsor.

(6) Published studies of other members of the pharmacological class of the drug.

(7) All additional significant safety findings about the drug from other sources.

(n) *Significant chemistry, manufacturing, and control changes, including microbiological changes (if applicable).* The DSUR must include a summary of significant chemistry, manufacturing, and control changes, including microbiological changes (if applicable), made during the reporting period to the investigational drug and must briefly describe the safety significance of the identified changes.

(o) *Protocol modifications.* The DSUR must briefly describe each significant modification made on behalf of the sponsor to protocols for phase I clinical investigations being conducted with the drug that were not previously reported under § 312.30.

(p) *Investigational plan.* The DSUR must contain a description of the general investigational plan for the coming year to replace the plan submitted 1 year earlier. The description of the general investigational plan must contain the

information described in § 312.23(a)(3)(iv).

(q) *Log of outstanding business.* The DSUR may, at the option of the sponsor, include a log of any outstanding business concerning the IND for which the sponsor has requested a reply, comment, or meeting.

(r) *Late-breaking information.* The DSUR must describe any potentially important safety information about the investigational drug or the clinical investigations conducted under the IND that was identified by the sponsor during preparation of the DSUR and after the data lock point.

(s) *Overall safety assessment.* (1) The DSUR must provide an overall safety assessment that is a concise, integrated evaluation of all new clinical, nonclinical, and epidemiological safety information obtained about the drug by the sponsor during the reporting period relative to the sponsor's prior knowledge of the drug, including knowledge obtained by the sponsor during any prior reporting periods. The assessment must include an evaluation of the risks associated with use of the drug that includes an interpretation of new safety information relative to the safety information that was previously obtained by the sponsor. The overall safety assessment must include the following items:

(i) Findings that suggest a significant risk in humans exposed to the drug, with any associated laboratory values, and relationship to dose, duration, or time course of exposure, if known.

(ii) Significant changes in information concerning adverse events that were identified in a previous DSUR.

(iii) Deaths that were previously included in an IND safety report required in § 312.32.

(iv) Subjects who withdrew from a clinical investigation because of an adverse event.

(v) Findings that suggest a significant risk to specific populations.

(vi) Drug overdose, misuse, and abuse cases or findings regarding the potential for abuse to occur.

(vii) Risks associated with long-term exposure.

(viii) Risks associated with the method of administration of the drug, diagnostic procedures related to use of the drug, or other procedures described in a protocol.

(ix) Evidence of clinically significant medication errors.

(x) Drug interactions.

(xi) Any other risks that significantly affect the safety assessment of the drug.

(2) The overall safety assessment must describe the balance between benefits, including theoretical or anticipated benefits, and cumulative identified risks related to use of the drug. The overall safety assessment must also describe changes to the benefit-risk profile compared to the previous DSUR, based on information obtained during the reporting period.

(t) *Summary of important risks.* The DSUR must provide a cumulative listing, along with a brief description, of all the important known risks and potential risks associated with use of the drug identified by the sponsor during the course of clinical and nonclinical investigations of the drug conducted on behalf of the sponsor. The listing must include a description of each risk. Risks identified by the sponsor in a prior reporting period must be re-evaluated annually, and their descriptions must be updated with any new risk information obtained during the reporting period.

(u) *Conclusion.* The DSUR must briefly summarize the following information:

(1) All changes to the sponsor's previous knowledge of the investigational drug's efficacy and safety resulting from information obtained during this reporting period.

(2) An outline of actions that have been taken by the sponsor during the current reporting period to address emerging safety findings.

(3) All additional actions that will be taken in the future by the sponsor to address emerging safety findings, to the extent known.

Dated: November 29, 2022.

Robert M. Califf,

Commissioner of Food and Drugs.

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DEPARTMENT OF COMMERCE

National Oceanic and Atmospheric Administration

50 CFR Part 679

RIN 0648–BL42

Extension of Public Comment Period for Amendment 123 to the Fishery Management Plan for Groundfish of the Bering Sea and Aleutian Islands Management Area (BSAI FMP); Bering Sea and Aleutian Islands Halibut Abundance-Based Management of Amendment 80 Prohibited Species Catch Limit

AGENCY: National Marine Fisheries Service (NMFS), National Oceanic and Atmospheric Administration (NOAA), Department of Commerce (DOC).

ACTION: Notice; extension of public comment period.

SUMMARY: On November 9, 2022, the National Marine Fisheries Service published a Notice of Availability and request for comments on Amendment 123 to the Fishery Management Plan for Groundfish of the Bering Sea and Aleutian Islands Management Area (BSAI FMP), but inadvertently did not include the supporting Amendment text. With this notice, NMFS is extending the public comment period by 60 days to February 7, 2023, to afford the public with additional time to provide comments on Amendment 123.

DATES: Comments on Amendment 123 and supporting documents must be received by February 7, 2023 as specified under **ADDRESSES**.

ADDRESSES: You may submit comments, identified by NOAA–NMFS–2022–0088, by any of the following methods:

- *Electronic Submission:* Submit all electronic public comments via the Federal eRulemaking Portal. Go to *https://www.regulations.gov* and enter NOAA–NMFS–2022–0088 in the Search box. Click the ''Comment Now!'' icon, complete the required fields, and enter or attach your comments.
- *Mail:* Submit written comments to Josh Keaton, Acting Assistant Regional Administrator, Sustainable Fisheries Division, Alaska Region NMFS, Attn: Records Office. Mail comments to P.O. Box 21668, Juneau, AK 99802–1668.

Instructions: Comments sent by any other method, to any other address or individual, or received after the end of the comment period, may not be considered by NMFS. All comments received are a part of the public record and will generally be posted for public viewing on *www.regulations.gov* without change. All personal identifying information (*e.g.,* name, address), confidential business information, or otherwise sensitive information submitted voluntarily by the sender will be publicly accessible. NMFS will accept anonymous comments (enter ''N/A'' in the required fields if you wish to remain anonymous).

Electronic copies of Amendment 123 and the final Environmental Impact Statement/Regulatory Impact Review (collectively referred to as the ''Analysis'') prepared for this proposed rule may be obtained from *https://www.regulations.gov.* The Analysis may also be found on the Alaska Regional Office website at: *https://www.fisheries.noaa.gov/resource/document/final-environmental-impact-statement-bering-sea-and-aleutian-islands-bsai-halibut.*