

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852
Submitted: <https://www.regulations.gov>

Re: Docket No. FDA-2020-N-0258
“Investigational New Drug Application Annual Reporting; A Proposed Rule”

March 8, 2023

To whom it may concern:

The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center) appreciates the opportunity to comment on the Food and Drug Administration (FDA)'s request for input and comments on the proposed rule entitled, “Investigational New Drug Application Annual Reporting; A Proposed Rule,” published in the Federal Register Vol. 87, No. 236, on Friday, December 9, 2022. It is timely and helps to harmonize the FDA regulations with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines.

The MRCT Center is a research and policy center that addresses the ethics, conduct, oversight, and regulatory environment of international, multi-site clinical trials. Founded in 2009, it functions as an independent convener to engage diverse stakeholders from industry, academia, patients and patient advocacy groups, non-profit organizations, and global regulatory agencies. The MRCT Center focuses on pre-competitive issues, to identify challenges and to deliver ethical, actionable, and practical solutions for the global clinical trial enterprise. While the MRCT Center often collaborates and interacts with FDA, we have not discussed the comments provided herein with anyone at FDA. The responsibility for the content of this document rests with the leadership of the MRCT Center, not with its collaborators nor with the institutions with which its authors are affiliated.*

The proposed rule is intended to replace the current annual reporting requirement (21 CFR 321.33) with a new, more extensive report, the annual FDA development safety update report (FDA DSUR), aligned with the ICH E2F guideline. While the ICH E2F is a guideline, not a regulation, the intention when that guidance was adopted was to harmonize the format and content for periodic safety reporting during clinical trials. The goal was to ensure that a single DSUR, including all safety data from all clinical trials conducted with a single drug, inclusive of different indications, different dosages and routes of administration, and different populations, would be prepared. The intention of alignment of the reports' scope and content for the same trials carried out in different regions was to ensure that submitted DSURs were comparable, that

* Brigham and Women's Hospital, Ropes and Gray LLP, Harvard Medical School, and Harvard University.

the analyses of safety data were comprehensive, and that regulatory agencies had (essentially) the same information available to them. The intention of FDA to bring the form and substance of the DSUR into alignment will reduce the burden of report preparation, provide more comprehensive and integrated information as proposed (§ 312.33), and allow sponsors and regulatory agencies—and IRBs, investigators, and others—to focus on decisions impacting the health and welfare of clinical trial participants.

The proposed rule will likely increase the burden of annual reporting for Investigational New Drug (IND) sponsors that are not currently submitting DSUR reports (e.g., biotechnology companies), but the increased burden is more than offset by the expected, potentially significant, safety benefits. Annual reports that accumulate safety information from a wide variety of sources (including clinical and non-interventional studies, and marketing experience) and that track knowledge about each safety issue through time are likely to contribute to earlier and more accurate identification of safety issues.

The MRCT Center particularly appreciates the detail and instruction of the proposed rule; we commend FDA and endorse the proposed Rule in this regard. In the context of enthusiastic support for the Rule proposed by FDA, there are two issues and a few questions that we wish FDA to reconsider:

Scheduling and timing of annual reports

In addition to format and content, the intention of ICH E2F was also to align the *scheduling* of annual reports. A single DSUR could then be shared across regulatory agencies containing a comprehensive picture of the investigational drug's safety profile *and* shared at the same time, thus enabling regulators to deliberate, discuss, collaborate, and/or rely upon one another should it be helpful. Viewing essentially the same data (and essentially the same cut of the same data) simplifies and streamlines these discussions.

The DSUR reporting period is tied to the “Development International Birth Date” (DIBD) (the date of the sponsor's first authorization to conduct a clinical trial in any country worldwide). The DSUR should be submitted to all concerned regulatory authorities no later than 60 calendar days after the **DSUR data lock point**, which is the last day of the one-year reporting period which starts on the DIBD.†

In contrast, the FDA DSUR reporting period is tied to the date that the IND went into effect. The FDA DSUR must be submitted to the FDA no later than 60 calendar days after the **FDA data lock point (DLP)**, which is one calendar day before the anniversary of the date the IND went into effect. The reasons for selecting a definition that differs from the DIBD are unclear.

† If clinical trials continue after product marketing approval, the sponsor can further choose for the DIBD to coincide with the International Birth Date (IBD).

In practical terms, for sponsors conducting multi-jurisdictional studies, the varying reporting periods would necessitate generating two separate annual reports covering the same data, but for different time periods. While FDA has proposed **waivers** from the proposed § 312.33 to address the varying reporting periods, (e.g., to permit the timing of annual FDA DSUR submission to align with the timing of DSUR submissions in other countries), the fact that sponsors must request a waiver (and whether a waiver must be requested annually or with some periodicity to maintain the altered date) appears unnecessarily burdensome. A preferred alternative would be to **build this flexibility into the regulation for sponsors conducting clinical trials in multiple jurisdictions (e.g., by allowing a shortened first-year report followed by syncing of dates) or defer to the ICH standard.** This will avoid uncertainty and time/effort involved in filing waivers, and, given the likelihood that sponsors conduct multi-jurisdictional clinical trials, the need for a waiver would be expected versus exceptional.

There are affirmative reasons for FDA alignment with the DIBD. First, international regulatory agencies would have access to the same data, permitting regulators to compare their analyses and discuss their decisions if questions arise. Second, it would promote reliance on monitoring, auditing, and inspections by regulators, easing the burden on regulators (and sponsors) if such reliance were welcomed. It would streamline reporting and enhance predictability.

The flexibility envisioned by FDA would not be compromised: sponsors would have the option to request a waiver from the DIBD if different timing for DSUR submission were needed or preferred. Finally, the frequency of reporting is not compromised: if the US is the first country to issue an IND, the DLP becomes the DIBD. If the US follows another country, FDA will have its first FDA DSUR earlier, not later, than it would have under the current proposal and would benefit from the earlier review of the product safety profile worldwide.

Sponsor-investigator

The current IND annual report requires information about clinical investigations of the investigational drug under a single IND. In contrast, the proposed FDA DSUR requires reporting of information about all clinical investigations conducted anywhere in the world on behalf of the sponsor evaluating the drug, including clinical investigations not conducted under an IND. Given the expanded scope of reporting and recognizing that sponsor-investigators (conducting investigator-initiated trials) generally do not have access to information about studies sponsored by the drug manufacturer under separate INDs, the proposed rule appropriately limits the information that must be provided by sponsor-investigators. Specifically, the proposed rule provides that: "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."

In our experience, drug manufacturers may provide financial, product, or in-kind support to a researcher for investigator-initiated or collaborative research, and the manufacturer may

contemplate or expect that it may use the data to support its own marketing application for the drug. Therefore, we would suggest clarifying that the limitation applies where the clinical investigation is not intended to support a marketing application **submitted by the sponsor-investigator**. Additionally, although this limit helps alleviate much of the burden of the expanded reporting requirements under FDA DSUR, we would still expect that the DSUR will be more time intensive for sponsor-investigators.

Additional minor questions:

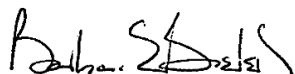
There are a few additional minor questions that would benefit from clarification in the proposed rule or accompanying guidance:

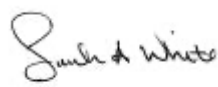
- For the tabulation of such cumulative exposure by age, sex, and race, can the sponsor submit tables similar to those reflected in ICH-E2F Tables 2, 3, and 4?
- For each individual investigation, can the sponsor prepare separate tables for each individual study to reflect the study subjects' age, sex, and race, or must they be pooled?
- In consideration of serious adverse events:
 - If clinical trials in the development of the product begin in countries other than the US, should reporting of SAEs from those countries be included (despite their occurrence in advance of study initiation in the US)? Must they be reported? Can a sponsor choose to include them?
 - In the rare event of unblinded subjects, may the sponsor submit the list of assignments for serious adverse drug reactions (SADRs) as an attachment, or must it be included in the body of the report?


Thank you again for the opportunity to comment on this important issue. We believe that the FDA has taken an important step in aligning the FDA DSUR with the ICH E2F guideline. The suggestion to align with the DIBD, while permitting alternatives, the additional consideration of sponsor-investigator responsibilities, and the minor clarifications of the additional questions will advance regulatory harmonization, streamline reporting, and decrease the burden, protecting the health and safety of participants.

Please feel free to contact the MRCT Center (bbierer@bwh.harvard.edu, sawhite@bwh.harvard.edu, or mark.barnes@ropesgray.com) if we can be helpful or you wish to discuss.

Respectfully submitted,


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