Biocom California

March 8, 2023

Dockets Management
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Re: Investigational New Drug Application Annual Reporting (FDA-2020-N-0258)

Submitted electronically

Dear Sir/Madam:

Biocom California appreciates the opportunity to offer comments on the Food & Drug Administration's (FDA) proposed rule on Investigational New Drug Application Annual Reporting[1].

Biocom California is the largest, most experienced leader and advocate for California's life science sector, which includes biotechnology, pharmaceutical, medical device, genomics and diagnostics companies of all sizes, as well as research universities and institutes, clinical research organizations, investors and service providers. With more than 1,700 members dedicated to improving health and quality of life, Biocom California drives public policy initiatives to positively influence the state's life science community in the research, development, and delivery of innovative products. California's life sciences industry generates over $375 billion in annual economic activity, supports 435,000 jobs, and increases labor income by $115 billion per year[2].

We commend the agency on its ongoing efforts to foster international harmonization of regulatory requirements. In the proposed rule, we appreciate that the proposed development safety update report (DSUR) requirements for investigational new drug (IND) annual reporting are consistent with the format and submission content of the DSUR supported by the International Council for Harmonisation (ICH). This annual reporting process will reduce burden and increase efficiency for sponsors supporting multiple submissions with one uniform format to the FDA and other regulatory authorities in the European Union (EU) and beyond. **In general, Biocom California supports regulatory harmonization efforts and many of the proposed changes to the IND annual reporting requirements for investigational drugs. We offer comments in the following areas:**

[1] Federal Register, 87 FR 75551, pp. 75551-75569, December 9, 2022.
[2] Biocom California 2022 Economic Impact Report Databook. https://www.biocom.org/eir/

Product Types Subject to Proposed Requirements

The proposed rule frequently mentions 'investigational drugs' with INDs as they relate to the FDA DSUR requirements. However, the rule does not specify whether these proposed requirements would also be applicable to other products that are subject to IND regulation. **We do not believe the proposed FDA DSUR requirements should apply to in vitro diagnostic (IVD) devices regulated as Biologics License Applications (BLAs) when indicated for donor screening and subject to IND regulations.** The proposed requirements are based on ICH pharmaceutical guidelines and do not consider product characteristics of IVDs. For example, the use of 'exposure' as mentioned in proposed § 312.33(j)(1), "subjects exposed to the investigational drug," and proposed § 312.33(j)(2), "patients' cumulative exposure," may not be applicable to IVD products. **We provide the following three recommendations for annual reporting requirements for IVDs regulated as BLAs and INDs:**

1) **Exempt device biologics, including IVDs for donor screening, from the proposed rule and allow sponsors of these products to maintain the existing reporting requirements in 21 Code of Federal Regulation (CFR) § 312.33, Annual reports[3], or**
2) **Exempt device biologics, including IVDs for donor screening, from specific elements of the proposed rule that are only applicable to drugs, and**
3) **Clarify which proposed FDA DSUR requirements are only appropriate for drugs and which requirements would apply to both drugs and IVD products.**

Sponsor Reporting Burden

For device biologics, the proposed FDA DSUR requirements will significantly increase the administrative burden for IND annual reports since the proposed provisions are more substantial than the current reporting requirements under § 312.33. In order to transition to the proposed DSUR format, sponsors will have to considerably modify current quality system procedures to align with the revised requirements. For sponsors of device biological products, there is no benefit from harmonization to the ICH pharmaceutical guidelines as these products are regulated as medical devices outside the United States and subject to international medical device/IVD regulatory requirements.

For investigational drugs, the proposed FDA DSUR requirements reduce duplicative regulatory efforts for sponsors currently utilizing the DSUR format. **However, for sponsors who will need to transition to the DSUR format, we believe some elements of the following proposed FDA DSUR requirements may be burdensome. In these cases, we ask the FDA to clarify that sponsors can provide the information historically reported and, in the situation where the agency has additional questions or would like more specific regional information, sponsors can provide those reporting elements upon request.**

- **Proposed § 312.33(s)(1)**: The requirement to provide a summary of nonclinical and epidemiological safety information.

[3] 21 CFR 312.33. https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-312/subpart-B/section-312.33

- **Proposed § 312.33(k)(1)(i)**: The requirement to further identify serious and unexpected suspected adverse reactions (SUSARs) in addition to reporting serious adverse reactions (SARs).

- **Proposed § 312.33(j)**: The requirement to report investigational drug exposure with tabulated demographic data for both ongoing and completed studies; as opposed to only providing this information for completed studies.

On page 12, the E2F Development Safety Update Report FDA guidance states: "The cumulative number of subjects from ongoing and completed clinical trials; the number exposed to the investigational drug, placebo, and/or active comparator(s) since the DIBD (Note: When treatment assignment is blinded, numbers of subjects can be estimated based on the randomization scheme[4]." The guidance currently facilitates greater reporting flexibility than proposed § 312.33(j) by recommending sponsors report the number of blinded subjects enrolled.

- **Proposed § 312.33(n)**: The requirement to summarize the safety impact of significant chemistry, manufacturing, and control changes.

- **Proposed § 312.33(i):** The requirement to report 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 for each ongoing and completed clinical investigations conducted during the reporting period.

This proposed requirement necessitates a greater level of detail for reporting study subjects than the current guidelines provided in the E2F Development Safety Update Report FDA guidance document.

- **Proposed § 312.33(k)(1)(iv) and § 312.33(s)(iv)**: The requirement to report a list of subjects who withdrew from a clinical investigation during the reporting period because of an adverse event.

The inclusion of a subject identification number in subject-level listings may be considered an identifier and we suggest that the FDA remove subject-identifying information from the requirement. Additionally, it is unclear whether 'clinical investigation' in proposed § 312.33(k)(1)(iv) and § 312.33(s)(iv) is referring to subjects who withdraw from the entire study itself or discontinue the study's investigational treatment. **We ask that the agency please clarify this language in the final rule.**

[4] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e2f-development-safety-update-report

Compliance Timeframe

Biocom California believes the proposed 180-day compliance date for any final rule is insufficient for sponsors to fully transition to reporting the FDA DSUR requirements since the proposed elements are significantly more detailed than the current IND annual reporting requirements under § 312.33. Sponsors will need to make considerable modifications to quality system procedures and implement subsequent training for personnel to ensure alignment with the revised requirements. **Therefore, we recommend that the agency provide sponsors with 240 days to fully comply with the finalized annual reporting requirements.** This timeframe would allow sponsors 120 days to make the necessary changes within their quality system, and an additional 120 days to complete and submit the necessary reports.

General Comments

In section B. Summary of the Major Provisions of the Proposed Rule, proposed § 312.33(i) "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." The proposed provision "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." **With respect to ongoing blinded studies, it is unclear how proposed § 312.33(i) would maintain clinical study data integrity since the estimation of subjects enrolled in treatment arms may require the embedding of data (i.e., hardcoding) directly into analysis programs. This practice may impact the ability to maintain data integrity as described in 21 CFR § 11 and we ask the agency to reconsider the requirement for study subject estimations for ongoing blinded studies[5].** Furthermore, disclosing certain safety and effectiveness information, with respect to interim analyses (proposed § 312.33(*l*)) and Data Monitoring Committee recommendations (proposed § 312.33(g)), for ongoing studies could negatively impact trial conduct. **We suggest that the FDA provide more context to sponsors regarding these requirements and clarify its reporting expectations for safety and effectiveness summaries for ongoing studies.**

In Table 1 § 312.33, *Nonclinical studies and findings*, proposed § 312.33(m) "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." It is unclear whether a summary would be needed for existing safety findings or new safety findings identified in the publications. **We suggest that the FDA clarify when a summary of safety findings is required and whether new, existing, or both types of safety considerations should be included in the summary.**

[5] 21 CFR 11. https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-11

In Table 1 § 312.33, *Summary of important risks*, proposed § 312.33(t) "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" and "requires an update of the risks identified in a prior reporting period with any new risk information obtained during the current reporting period." **We appreciate the flexibility in assessing risk and, in order to better understand the FDA's reporting expectations for this proposed requirement, we ask that the agency publish a template or provide examples to sponsors outlining the level of detail and format for reporting safety/risk-related information in the DSUR**.

We appreciate the opportunity to provide feedback on behalf of our members and thank you for your time and diligence in examining our comments. Please contact Biocom California's Associate Manager of Regulatory Policy, Zoe Bilis, at zbilis@biocom.org for additional information or questions. We look forward to continuing to work with you on this matter.

Sincerely,

Joe Panetta
President and CEO
Biocom California