August 25, 2019

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852


Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments regarding the New Drug Regulatory Modernization: Improving Approval Package Documentation and Communication.

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial, and environmental biotechnology products.

BIO appreciates the FDA’s goal of providing greater clarity on FDA’s application review and decision-making process. We commend FDA’s efforts to modernize the New Drug Regulatory Program through the use of: (1) The Clinical Data Summary Pilot Program (Pilot), through which parts of a Sponsor’s clinical study reports (CSRs) are posted and (2) a new integrated template that will be used to document FDA’s review of new drug applications and efficacy supplements. BIO commends the Agency’s efforts to improve transparency in the drug approval process and believes increased transparency will ultimately benefit patients, BIO member companies themselves make strong efforts to support clinical trial transparency by posting protocols and results and sharing data consistent with the Final Rule on Clinical Trial Registration and Results Information Submission. BIO strongly supports the new integrated review process and template and agrees that this format will also clarify and improve communication between FDA and the Sponsor, as well as provide new insights regarding FDA’s regulatory decision making.

The FDA has stated it is considering where to focus its efforts to increase transparency around the drug approval process: either on the development of new integrated review documents, or on the release of CSRs (as seen in the Clinical Data Summary pilot). For the following reasons, we believe that the greatest benefit would be achieved by focusing on the new integrated review template:

(1) The release of CSRs, while commendable, would not give stakeholders any additional significant insights to the comprehensive Agency’s assessment of benefit-risk.

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(2) The clinical protocol and statistical analysis plan, which were also in-scope for release under this initiative, are already made public by Sponsors on ClinicalTrials.gov, following study completion.¹

(3) Additionally, given that other countries are engaging in their own transparency initiatives involving publication of clinical data, a subset of CSRs would still be available even if the FDA did not routinely publish them.

Below we offer the following comments pertaining to both the integrated review and the Pilot for FDA’s consideration:

A. Integrated Review Process:

1. How does the new format of the integrated review inform your knowledge of FDA’s basis for making decisions?

As mentioned above, BIO believes that the use of the integrated review provides greater clarity regarding the FDA’s regulatory decision-making. The integrated review also provides the added benefit of enabling stakeholders the ability to review results from multiple studies, side-by-side.

As FDA is considering information that may be provided in appendices instead of the summary or the integrated assessment section of the review template, we request that the FDA consider including information related to proprietary name review and clinical inspections in the appendices to support and facilitate FDA’s efforts to streamline the review template. To remove redundancy, we also encourage FDA to streamline background information that is included in several places within the documents, perhaps into a single location. For example, it would be helpful for the background of the disease and the drug, class of drugs, route of administration, mechanism of action, among other items to be consolidated in one place in the integrated review document. BIO also requests that Administrative and Correspondence documents, reflecting the administrative record, also continue to be made available, if not included in the appendices. We emphasize the importance of retaining reviewers’ assessments of issues that were identified during the review. These would support enhanced transparency and clarity on how the identified issues were resolved during the review process. Regulators around the world often rely on FDA’s findings and it is important that the findings of all relevant clinical studies be summarized and for FDA to indicate how those studies informed their decision making.

BIO also requests that the FDA clearly reference information on the review of drug development tools and new technologies (e.g., clinical outcome assessments (COA), patient reported outcomes, digital tools, and real-world evidence). For example, it is important to include whether any COA data was submitted by the Sponsor, whether (and why or why not) the COA data informed regulatory decision-making, was considered validated or “fit-for-purpose,” and whether it was included in labeling. Lastly, it is important to retain information in

¹ Clinical Trials Registration and Results Information Submission, September 21, 2016.
the integrated review related to key negotiations between the FDA and the Sponsor, such as labeling negotiations/details.

2. **How does the usability and accessibility of information in the new integrated review compare to the original review posted on FDA’s website?**

FDA’s new integrated review template constitutes an improvement over the older template, as it is easier to navigate and information on benefit-risk assessments is displayed in a more clear and concise manner. This new review template allows for the clear delineation of FDA’s rationale for the approval. This clarity would likely help Sponsors better understand the Agency’s thinking and in turn could lead to stronger regulatory applications, more first cycle approvals, and ultimately benefit patients in need of new therapies. However, given current technology, we encourage FDA to consider providing the information included in the integrated review in an electronic format that can easily be searched across products. The ability to search across reviews increases shared learnings throughout the industry and has the potential to streamline drug development. In addition, FDA should consider making the new review template available in downloadable formats other than PDF. We understand, for example, that, in connection with the Office of New Drug reorganization, and FDA’s modernization efforts the FDA will be utilizing technology platforms that will facilitate review of similar issues across applications, improve accessibility to institutional knowledge based on existing reviews, and better support information sharing among review teams and across divisions. Other stakeholders looking at review information and decisions across review divisions likewise would benefit from being able to access this higher-level view through the use of updated technologies and media. It is unclear what tools, programs, or software FDA is using to facilitate its internal updates in this regard, so this request is not specific to what format (beyond PDF) should be used to publish the integrated reviews, but FDA might consider XML.

We request that the FDA also ensure that any relevant information is not removed or omitted as the new templates are drafted. There may be potential to inadvertently omit key information with the issue-focused approach to integrated review and template for topics which may not present an issue after appropriate review of data/information submitted by the Sponsor. BIO request that the FDA consider establishing mechanisms to ensure that all key information is captured in the template, even if it may not pose a question or raise an issue after review of the marketing application.

3. **How could the information provided in the new integrated review format be used, if at all?**

The information in the new integrated review format could be used to understand how individual trials were designed, the outcome measures used, and results of the studies. In addition, it is possible to understand at a submission-level how the information from the individual trials was used by FDA for regulatory decision-
making. Increased knowledge sharing may also help to decrease development burdens across industry. Additionally, we envision that the integrated review will provide insights to other regulators to be able to rely on FDA’s findings as they make their own regulatory decisions.

4. What do you believe would be the potential advantages and disadvantages of posting review documents in this format?

One advantage is that the new format includes key information that provides greater insight into FDA’s decision-making process. However, as mentioned above, there may be potential for the FDA to inadvertently omit key information with the issue-focused approach to integrated review and template for topics which may not present an issue after appropriate review of data/information submitted by the Sponsor. To this end, BIO request that the FDA consider establishing mechanisms to ensure that all key information is captured in the template or as appendices, even if it may not pose a question or raise an issue after review of the marketing application.

In order to facilitate broader communication and consistency of common information across regions and limit confusion for non-technical readers. BIO also recommends FDA develop a non-technical summary for non-technical readers and harmonize the format, to the extent permitted by US requirements, with the “lay summaries” required under the European Union-Clinical Trial Regulation.

5. Based on the integrated review, were the issues that concerned the review team clear and understandable? If so, what helped achieve this? If not, what can be improved?

BIO believes that the issues that concerned the review team are clear and understandable. The Table of Contents is clear as to the location of any review issues. However, as FDA implements the new integrated review, we encourage FDA to streamline the process for information requests and questions for the applicants during the marketing application review. We are hopeful that the integrated review process, including planned early and frequent interactions of the FDA review team, will address the challenge for Sponsors receiving multiple and often redundant information requests and questions from different disciplines during the application review. We understand that questions arise during the review process, and timelines need to be short to meet the PDUFA goal dates. Accordingly, we encourage the Agency to contact the Sponsor as needed with as many information requests and questions as appropriate and reasonable to inform their review, however, it may be more efficient and helpful for FDA to incorporate steps and checks in the integrated review process to consolidate information requests and questions when possible, to ensure they are not duplicative to similar information requests and/or questions already asked by another discipline during the application review, and to leverage the previously submitted information where appropriate.
6. Is there important information in the integrated review that is difficult to locate or should be added?

We caution the FDA to strictly limit deletions to the information repeated across review documents rather than information that FDA deems not to be important to external entities. Different stakeholders make use of FDA posted documents for different purposes, and FDA is not likely privy to all such uses. For example, FDA recently engaged in an effort to trim the content of publicly posted action packages, which led to the elimination of a significant number of meeting minutes. These documents for non-milestone development phase meetings, mid-cycle communications, and late-cycle meetings are important for stakeholders’ understanding of the evolution of FDA’s thinking during the development program and throughout the Agency’s review of an application. Likewise, administrative and correspondence documents should continue to be made available. In the spirit of maintaining transparency of FDA’s activity and decisions throughout drug development and review, BIO respectfully requests that FDA re-commit to including the minutes of all meetings held on a development program in the posted action packages.

As FDA is considering other information that may be provided in appendices instead of the summary or as a part of the integrated assessment section of the review template, we request that the FDA include information related to all major meeting minutes (e.g., pre-IND, EOP2, pre-NDA/BLA, meetings held during the marketing application review as well as any other meetings where important agreements are reached between the Sponsor and FDA), proprietary name review, and clinical. BIO also requests that the FDA provide in the appendices a summary of the regulatory exclusivity associated with the application (i.e., any FDA awarded exclusivity such as orphan drug, new chemical entity, pediatric exclusivity, etc.). Similarly, it would also be helpful if the FDA indicated the review designations (e.g., breakthrough therapy designation), as well as use or issuance of a priority review voucher. If the application under review is for a combination product, a summary of any human factors studies required by the Agency for approval should also be included.

In connection with the updated integrated review template, including earlier use of the benefit-risk framework as a leading, integral document, FDA also should consider how other information that influenced regulatory decision-making should be conveyed. In particular, with respect to the statement on patient experience data (i.e., the table current being used to reflect how patient experience data were used in the context of review), FDA should ensure that the approach to completion of that table, and other provision of patient experience data or patient-focused drug development efforts, is consistent across review divisions. Additionally, FDA should ensure the linkage between patient experience data provided or otherwise considered in the context of its review and regulatory decision-making is clearly reflected in both the benefit-risk assessment, as well as the statement on patient experience data. FDA’s improvements in this regard, to better convey how patient experience data and similar input (e.g., real-world
data) influence its decision-making should be made available to stakeholders in a clear, plain-language format, to ensure broad and equal utility for those who study, develop, prescribe, and/or take therapies regulated by FDA.

B. Clinical Data Summary Pilot Program

1. How did the CSR posted in this Pilot affect or compare with your understanding of the CSRs submitted to FDA by drug Sponsors?

2. How usable and/or accessible was the information in the CSR that was posted for the Pilot?

3. Did the required redactions/removal of certain information from the posted CSR affect your understanding or use of the posted information?

   The number of redactions were minimal and only affected the confidential/privacy-related content of the CSR. The redactions did not detract from the overall understanding of the report and appendices.

4. How might the information/content posted from this Pilot be used? What other information/content would have been helpful?

   The information provides insight into how a trial was designed, inclusion/exclusion criteria used, collected outcome measures, including all primary and secondary outcome measures, and provides more extensive results than those required to be posted on ClinicalTrials.gov.

5. Given the other review documents available (e.g., FDA’s action package), how did the posted CSR affect your understanding of FDA’s decision-making process regarding drug applications?

6. What do you believe would be the potential advantages and disadvantages of posting this information routinely?

   While one advantage of posting this information routinely is that it increases transparency, the posted information only covers pivotal trials that are included in a submission. For these pivotal trials that were filed to global regulators, the Pilot is a duplication of the documents posted in compliance with EMA Policy 0070 and Health Canada Public Release of Clinical Information, with a region-specific approach to ensure protection of personally identifiable information (PII) and company confidential information (CCI). Duplication of documents may cause confusion to those wishing to review, and releasing multiple versions of the same document in different regions, each with different standards to the protection of privacy information, may result in unintended information being released across the versions and could affect calculations of the risk of re-identification of individual participants. Similarly, in the context of small clinical trials and/or clinical trials for rare diseases, there is an increased risk that participants could be re-identified. While in the example document posted, some de-identification has been performed (e.g., subject ID numbers have been removed), there is no assurance that the document is truly...
anonymized, and there are no terms of use in place (e.g., users must agree not to attempt to re-identify patients), thus potentially jeopardizing trial participant privacy.

Additionally, CSRs may contain commercially confidential information. Although in the example posted, FDA has redacted some information that may potentially be commercially confidential, there is no indication that Sponsors will be given the opportunity to review redactions or justify additional redaction before the documents are made public. This is inconsistent with the principles that FDA applies when implementing Freedom for Information Act requests (21 CFR 20.61(e)), which provides Sponsors an opportunity to object to disclosure and to state the bases for its objection, in order to protect a Sponsors’ intellectual property rights and further commercial development.

7. **Is there any additional information you would like to provide regarding the potential benefits or risks, resource requirements, and international challenges of publicly releasing a limited number of sections from certain CSRs at the time of marketing approval?**

BIO recognizes that different regional laws and requirements related to the identification of PII and CCI make it challenging to develop a single version of a releasable document that would be consistent across all regions. However, a single global version of each document would not only be more efficient to produce but would also likely be less confusing to those wishing to review the material, as a consistent version of each document would be released globally. BIO encourages FDA to consider aligning these documents to the extent possible by law. Additionally, other regulatory authorities that publish CSRs after marketing authorization, including the European Union and Canada have put in place terms of use prohibiting unfair commercial use and prohibiting any attempts to re-identify trial participants. BIO encourages the FDA to consider such terms if this work advances. Alignment with other regions would work to improve the consistency of globally published trial data and documentation, which would likely increase the public’s confidence in transparency initiatives and in drug developers as a whole.

BIO appreciates this opportunity to submit comments regarding New Drug Regulatory Program Modernization: Improving Approval Package Documentation and Communication. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/
Danielle Friend, Ph.D.
Director, Science and Regulatory Affairs
Biotechnology Innovation Organization