Docket No. FDA-2019-N-2012 for "New Drugs Regulatory Program Modernization: Improving Approval Package Documentation and Communication."

Access: https://www.federalregister.gov/documents/2019/06/27/2019-13751/new-drugs-regulatory-program-modernization-improving-approval-package-documentation-and

To access the docket to read background documents or comments received, go to https://www.regulations.gov and insert the docket number into the "Search" box and follow the prompts.

Read the Supplementary Information Section (situated below the general information on how to access the docket).

A. Regarding the Clinical Data Summary Pilot Program

See the CSR posting available on FDA's Clinical Data Summary Pilot Program web page at https://www.fda.gov/drugs/developmentapprovalprocess/ucm589210.htm

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

SH/AG Response: As clinical research professionals working within the industry, our understanding matches our working knowledge and expectations. The CSR posted is consistent in format, structure, and content, with CSRs we typically prepare for submission to FDA.

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

SH/AG Response: The posted CSR was clear and well-presented; however, as the posted version was in a PDF version, it was not as navigable as one which would be submitted through the eSub Gateway. For example, some of the links to Appendices and supportive documents (e.g., IDMC Charter) do not appear functional.

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

SH/AG Response: No – the redactions do not affect our understanding and seem reasonable, from the perspective of regulatory medical writing professionals working in the field. Examples are: Redactions within Section 3.4.1 'Formulation Information' and 3.4.2 'Issues Identified etc', seem reasonable to protect Commercially Confidential Information (CCI) interests, and do not affect data utility. Redactions within narratives in Section 7.2.3.1, the Section 7.2.3.4.x series, Section 7.3.3 are appropriate to protect subject identity, and redactions within the substudy, Listings (page 851 forwards), are appropriate, obscuring date of ECG, Subject #, etc. All such redactions are as we would expect, protect subject identity, and do not affect data utility.

Notably, staff names (that would otherwise not be publicly available) are not redacted e.g., page 17 'Study administrative structure' names all Sponsor staff; page 136 'Signature of SRMO' names all the report contributors. Such names could have been redacted without loss of document utility. Careful balance between transparency and protecting the identity of those engaged in the conduct and reporting of trials is necessary.

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

SH/AG Response: The CSR can be used to help guide drug development programs and study designs for similar products. Posting of the protocol is very helpful. For example, see Protocol page 16 of 113 where the Protocol Amendments summary and reasons for Amendment 8 are given. This shows that the statistical planning had to be substantially revised because the study was originally underpowered. The included detail is valuable for those involved with similar studies at the planning stage. By also posting the statistical analysis plan (SAP), the actual statistical methodological detail is available. Such knowledge could save other developers going up 'blind alleys' in terms of study design and statistical planning from the outset.

In our opinion, the posted documentation is adequate. However, if there are characteristics unique to that therapy or indication, there should be commentary from the Agency. No other information/content than that already posted would be required. Such resources - if accessible by the public as well as medicines developers - contribute positively to an environment of public trust, and have potential to improve efficiency and reduce costs associated with medicines development. As public disclosure of these documents is already mandated in the EU and Canada, pursuing the same route and documents for disclosure would minimize the burden on medicines developers.

We are not sure that there is a significant advantage of posting the full (redacted) CSR versus the Integrated Review (IR). The latter provides the critical data, as well as in-context FDA thinking. In terms of drawing one's own conclusions, perhaps the full CSR would be of greater value; however, the IR is more digestible (being ¼ the length) and provides added value. If FDA's question is whether to expend energy on developing an IR template, we know that FDA prepares this type of document as part of their "Action Package" (formerly known as Summary Basis of Approval – SBA) but this is not publicly disclosed. The latter would contribute toward greater transparency re: the relationship between the FDA and Pharma. As with current policy, should a party have a legitimate reason to request the full CSR, they could apply to an independent adjudication committee for release of the document.

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?

SH/AG Response: In our view, the FDA's Action Package, if inclusive of the Integrated Review, provides the critical data, as well as in-context FDA thinking.

In terms of drawing one's own conclusions, perhaps the full CSR would be of nominally greater value; however, the IR is more digestible (being ¼ the length) and provides added value. Posting the IR contributes to greater transparency re: the relationship between the FDA and Pharma.

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

SH/AG Response:

Advantages:

a. Transparency and disclosure contributes to an environment of trust.

b. If FDA posting requirements were aligned with existing requirements in other jurisdictions (e.g., EMA and Health Canada CSR and clinical summary documents disclosure requirements), this would streamline transparency and disclosure activities across regions, and reduce the burden on Sponsors. It would also better ensure the consistency of information available to stakeholders, worldwide.

c. Publicly disclosed information - if used intelligently by medicines developers - can streamline development of similar products, thereby contributing to earlier patient access to those products.

Disadvantage:

a. Potential for inflating product development costs, such as those associated with redaction, which may be passed directly onto patients and to governments of countries with social healthcare systems. However, efficiency gains resulting from developers having access to vetted study designs and statistical methodologies can reasonably be considered to outweigh costs associated with public posting activities.

NOTE: A possible alternative would be to post the protocol and the IR, making the CSR available, upon request. This might reduce the burden associated with providing a redacted CSR and give the reader the most meaningful information. Whether this would satisfy those who distrust the Pharma-Regulator partnership in terms of not disclosing potentially "harmful" information, remains a consideration.

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?

SH/AG Response: Please see responses to the questions above, which describe these considerations.

Although FDA does not specify which CSR sections are to be released, these may be selected based on criticality to the therapeutic index. It remains to be determined whether this selection will be initiated by the Sponsor, by FDA, or as a collaborative effort. We believe that the same purpose might be served by publishing the IR, given that it would provide rationale for the importance of the particular data subsets upon which the approval/non-approval is founded.

In summary, if CSRs, protocols, and SAPs are to be publicly disclosed then it would be greatly beneficial for FDA to align requirements with EMA and Health Canada, to minimize the cost and effort burden on Sponsors. For documents already publicly disclosed in those other jurisdictions, an electronic link only to them, within the FDA platform, could be a pragmatic alternative to having to post the actual documents. Any similar streamlining effort would be welcomed.

To illustrate the new integrated review template, the original reviews for NDA 210806 (PIFELTRO (doravirine) tablets, 100 milligrams (mg)) and NDA 210807 (DELSTRIGO (doravirine, lamivudine, and tenofovir disoproxil fumarate) tablets, 100/300/300 milligrams) have been rewritten to provide an example. The original multidisciplinary review for the NDAs and the information provided in the new integrated review template are posted on https://www.fda.gov/newdrugsmodernization#integrated

This is the link to the integrated review prepared by the FDA: https://www.fda.gov/media/128270/download

B. Regarding the Integrated Review

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

SH/AG Response: We appreciate the value of the (Integrated Review), a 183-page document, with 64 pages in the actual report; the remaining pages comprise Appendices. Appendices include a summary of the regulatory history; a summary of review studies submitted under the IND, including the preclinical studies; Protocol Synopses for the studies described in the main body; further detail on benefit data, including sensitivity analyses and subgroup analyses, from the main trials and a supporting trial; limited summary adverse events analysis, with focus on events of interest for the indication; summary laboratory results analysis; safety analysis by demographic subgroups; PRO analysis; and MoA and drug resistance additional information – in vitro, in vivo, and in treatment-naïve trials. There is a section on 'Labelling considerations and recommendations – additional information'. This describes the summary of major changes to the label. There is also a 'Financial disclosures' section that gives the Agency's assessment of whether or not the trial results were biased as a result of the disclosures. We intend that this summary of the IR assists the reader to place our comments below into context without having to directly access the IR.

Section 2 'Benefit risk assessment' table is very user friendly and allows the reader to quickly understand the elements and assessment rationale; the 'Conclusions and Reasons' column provides an excellent summary of FDA's assessment of the submitted package. The B:R Conclusions statement on page 9 is helpful for the lay public.

Throughout, a more frequent use of tables organized in a logical format (similar to those used for B:R) would enhance the reviewability and comprehension of the assessments. We found the tabular format to be much superior to one that is predominantly text-based.

Other sections, e.g. 6.2.3 SAP – are an SAP summary only, so there is loss of utilisable detailed information for statisticians wishing to leverage the detail into their own programs. However, the purpose of this report seems different than that of the transparency aim of disclosing clinical documents themselves, so is understandable that such information could be lost in such a heavily summarized document. The aim of this report is rather to show the public and Applicants how the Agency assessed the package, drew its conclusions, and therefore, granted or did not grant the medicine a license.

The breakdown of each issue into summaries of 'Issue', 'Conclusion' and 'Team Assessment' is helpful to aid wider understanding of these complexities and to communicate the Agency's view on each point. The 'Issues' are clearly and succinctly described. Over time, with disclosure of similar reports, more will be understood outside the Agency of the Agency's perspectives and methods for evaluating medicines submissions.

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

(This is the where the original review is posted: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210806Orig1s000,210807Orig1s000TOC.cfm)

SH/AG Response: Much of the content of the new template is populated from the 'Multi-Discipline Review/Summary, Clinical, Non-Clinical' PDF listed under FDA Application Review Files in the original review on FDA's website. The preclinical information included in the original document body is appended in the summary template, which streamlines the information and places focus on the human data. The template summary is more easily comprehended by the lay audience and is generally easier to navigate and is set out in a more user-friendly format than the original review posting. Also integrated into the template is the original B:R assessment, and this is written in a more readable way than in the original document.

The reduction of volume certainly contributes to a more readable assessment document; however, as noted above, the tabular format used in the B:R section of the IR would significantly contribute to reader comprehension and accessibility.

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

SH/AG Response: There are several possible ways of providing information in a pubic posting, with options including posting only the CSR, only the IR, or both. Often the value of information is lost if one has to plough through hundreds of pages of (primarily) text-based assessments. One could argue that the more summarized and, therefore, accessible information might be of greater value. If the full CSR is going to be posted or otherwise available, if necessary/desired, the

interested party could access that (either on-line, or by request). The purpose of the IR seems different than that of the transparency aim of disclosing clinical documents themselves. The aim of the IR is rather to show the public and Applicants how the Agency assessed the package, drew its conclusions and therefore granted or did not grant the medicine a license. So the information could be used to better understand the Agency's general thought process. The template could be a good replacement for the posting of CSRs and other clinical summary documents. If however, the CSR and summary documents are to be posted, the opportunity to align with other regions such as the EU and Canada would benefit global sharing of informational resources, and would show FDA to be a key player in the global initiative towards transparency and responsible clinical trial data sharing generally.

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

SH/AG Response: See response above.

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?

SH/AG Response: Yes, the 'Issues' were clearly set out and informative.

6. Is there important information in the integrated review that is difficult to locate or should be added?

SH/AG Response: The full protocol for each study in the IR could be appended, instead of only the synopses. Also, as suggested use of tabular formats throughout the IR would be highly beneficial.

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