

FDA's new integrated review template and implications for regulatory intelligence

By Emily Huddle

US Food and Drug Administration (FDA) review summaries, previously referred to as summary basis of approval documents, can serve as invaluable sources of regulatory strategy information, the details of which are not publicly available from any other source. When the FDA announced its plans to use a more streamlined approach to communicating regulatory decisions through an integrated assessment process and review document, it raised concern among those who contribute to and formulate regulatory strategies.

Introduction

Prior regulatory precedent is an essential factor for consideration when formulating a regulatory strategy for proposal to a regulatory health agency. Prior precedent not only provides valuable insights to drive planning of future strategy, it helps avoid repetition of past strategy failures. There are many publicly available sources for ascertaining prior strategy, including company press releases and presentations, advisory committee proceedings and associated documents, and, most importantly, marketing application review files. This article explains the various types of information that can be extracted

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from available review summaries to inform regulatory strategy, how to search across review summaries, and the impact of the FDA’s new integrated assessment template on information disclosed within the review documentation.

The new integrated assessment template

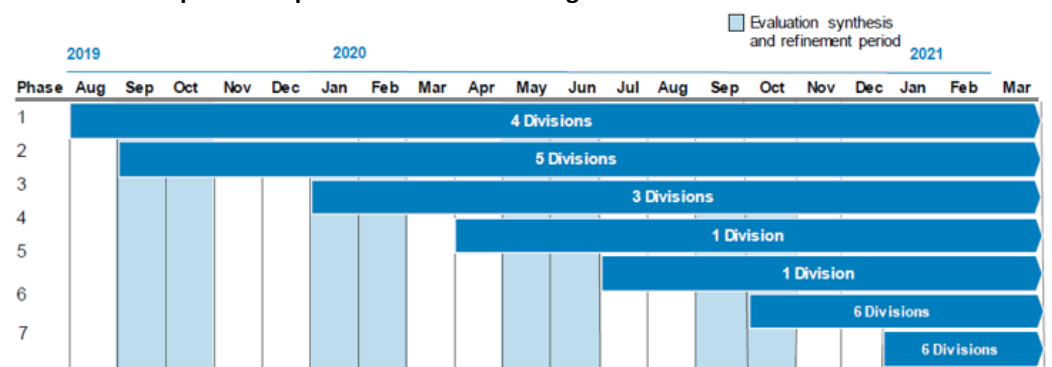
One of the six strategic objectives under the FDA’s Center for Drug Evaluation and Research initiative to modernize the New Drugs Regulatory Program, includes a new integrated assessment process.¹ The agency has described the overall objective of the integrated assessment as “critically, collaboratively, and consistently [assessing] whether information in drug approval applications meets legal and regulatory requirements.”¹ The integrated review is intended to focus on “application-specific issues, [using] a team-based interdisciplinary model, and increasingly [incorporating] the patient perspective to provide an integrated assessment.”¹

In June 2019, a new review template was introduced to support the integrated review process. It was intended to describe more clearly the agency’s basis for its regulatory decision. The FDA sought public feedback on the new template via a Federal Register notice² and provided three examples to illustrate how the new assessment approach would be documented within the new template, which would consist of an executive summary, interdisciplinary assessment, and appendices.

In October 2020, the FDA held a public workshop to seek additional feedback from stakeholders, as the agency had begun a phased implementation (**Figure 1**) of the new template to include new molecular entities, original biologics license applications, and select efficacy supplement reviews. At the time of the workshop, about eight reviews were publicly available using the new template.

Multiple review divisions and therapeutic areas were represented in the set of published examples, a mix of both standard and priority reviews, as well as inclusion of a fixed-dose combination products. The FDA requested stakeholder feedback to ensure the most useful information from product reviews was being retained; solicited recommendations for improvement and potential advantages

FIGURE 1 FDA’s phased implementation of the integrated assessment^{3,a}



^aEach evaluation period consists of feedback synthesis and subsequent refinement of trainings, process, and template.

and disadvantages; and enquired whether the new format clearly presented the FDA's benefit-risk determination and basis for its decision.

A variety of stakeholders were represented at the public workshop, including those from academia, patient advocacy groups, pharma trade associations, as well as representatives from individual pharma companies. During the workshop, it was consistently acknowledged that the new format was concise, the presentation of information was not duplicative, and that it enabled layperson comprehension. The stakeholder feedback overwhelmingly reflected the necessity for the agency to continue to communicate its decisions with sufficient transparency and allow the disclosure of pertinent details.

Finding the needle in the haystack

It is the disclosure of sufficient detail that helps regulatory sponsors in their understanding of precedent. Examples of information that can be extracted from review documents include: how real-world data were used to support an efficacy claim; how a safety signal was addressed to secure approval; the input and opinions of a specific reviewer; or the acceptability of drug development tools, such as a novel biomarker or clinical outcome assessment.

Review documents provide a level of detail starting with pre-IND (investigational new drug) to final approval that is not available from any other publicly available source. Although a company press release may include high-level information about the pivotal clinical studies to support an application and pertinent safety results, it is rare that further details are provided beyond the phase 2/3 study program. It is possible to cobble together information on a product development lifecycle strictly from company press releases and presentations, but it is time consuming and does not present a comprehensive timeline in the same way a review summary can.

Review documents published for original marketing approvals are typically hundreds, if not thousands, of pages in length. The prospect of finding specific examples across all published review documents seems akin to finding a needle in a haystack. Fortunately, there are regulatory intelligence databases that enable specific queries across thousands of published reviews. These databases, available from external vendors, allow for in-text searching for a string of search terms and other qualifiers, to return a list of product reviews that meet the search criteria. With this listing, additional analysis is still needed to extract the relevant details and further contextualize the examples, but overall, such databases enable a more straightforward discovery of those important "needles."

The limitations of database searches include the prior availability of electronic product review documents (before about 2000 is typically not available), public availability of supplemental reviews, and consistency in terminology used within the reviews. Inconsistency in terminology is not unexpected, whether across sponsors, review divisions, or centers, nor is the evolution of the terminology over the years. For example, while the overall concept of "real-world data" may not be entirely new, the current concept and implications to support regulatory

decision making has evolved into greater significance. So, a summary review that uses the term “real-world data” from 2019 has greater significance than a review package from 2004, if the need is to understand the FDA’s more contemporary acceptance of real-world data to support approvals.

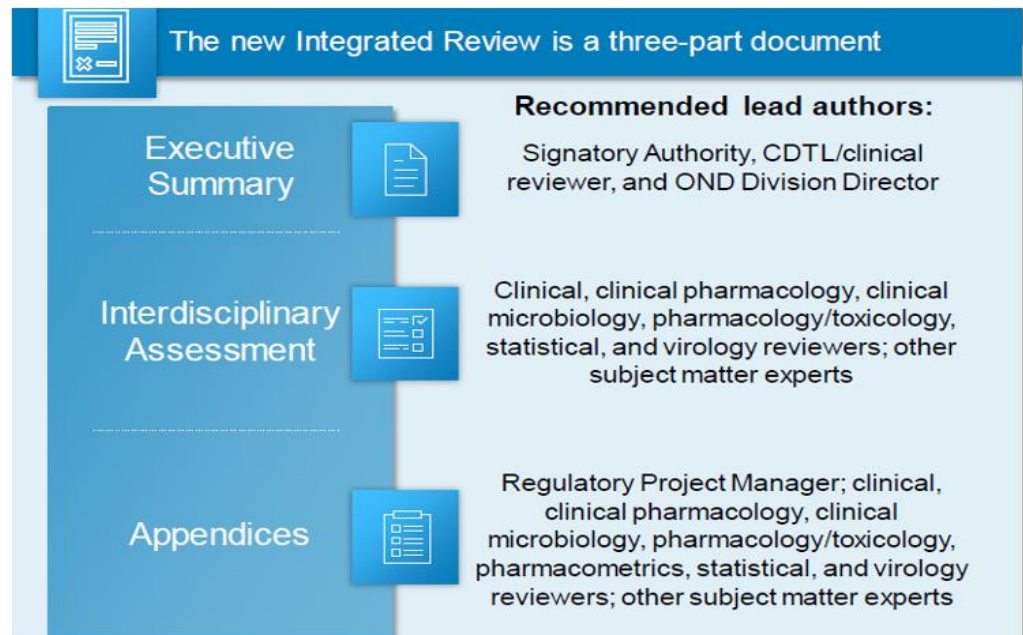
While the limitations of the databases and source documents are inherent, smarter search strategies can maximize the number of obtainable results. As inconsistency in terminology across the review packages is expected, it is important to modify search terminology and other search qualifiers to match all possible variations within the review packages. For example, “Is real-world data with a hyphen or without?” In addition, if less familiar with a specific concept, topic, or technology, it may be necessary to do preliminary background reading to establish a cursory understanding to develop more exact search terminology(-ies).

A simple addition or adjustment to a search strategy can sometimes make the difference between finding no results and finding relevant, supportive examples. It is of equal importance to understand how the examples of precedent will support a regulatory proposal when considering a search strategy and possible ways to further refine the results, for example, by proposed indication, a specific safety event, or anticipated review division or a specific reviewer.

Retaining adequate detail

The new integrated template consists of three main components: an executive summary, an interdisciplinary assessment, and appendices. A description of each section was presented at the October 2020 public workshop (**Figure 2**).

FIGURE 2 FDA’s new integrated review template⁴



While the executive summary and interdisciplinary assessment will help fulfil the FDA's modernization objective to more concisely communicate the benefit-risk assessment that informed its regulatory decision, the details disclosed within the appendices portion will be of more critical importance to regulatory sponsors.

Albeit an unassuming title, the "Administrative Documents" section of the previous, discipline-based review documents was a collection of loosely organized FDA forms and correspondence between sponsor and FDA that contained important insights into the progression of the development program and regulatory review. Standardized, checklist-style FDA forms indicating various characteristics of the application (e.g., expedited designations, first, second, etc. cycle approval) provided helpful details in the circumstance of collecting metrics for a set of approvals. Redacted meeting minutes (e.g., pre-IND, end of phase 2, and pre-new drug application) help provide insight into a proposed development program and its evolution to final execution. Significant details concerning sponsors' proposals, whether the FDA accepted or denied the proposal(s), and the reasons for such, along with the agency staff members providing input into the decisions, can sometimes be unearthed from correspondence included within this section. Issues that were subject to internal disagreement within the agency and the final outcomes are also valuable details to a regulatory affairs strategist or liaison. Likewise, e-mails between reviewer and sponsor before the receipt of a complete response letter or negotiation of a post-marketing commitment, also provide valuable insights to guide sponsors.

The FDA indicated its plan during the public workshop to include an addendum within the appendices section of the review template to include "work done that did not directly impact the decision-making process but may be helpful as a reference for future work." Details that may at first glance seem inconsequential to a consumer or healthcare provider readership, will likely provide a positive benefit to both industry and agency alike. Increased transparency of the details of regulatory review may result in fewer meeting requests from sponsors, if there is precedent available for similar approaches that also includes the FDA's acceptance or rejection of such approaches. As agency's thinking on a particular topic evolves, review proceedings provide insight into increased acceptance of more novel approaches as they change over time and/or within a review division. Conversely, knowledge of unsuccessful approaches or the FDA's rejection of certain approaches will prevent sponsors from proposing or repeating them, ultimately shortening development times and increasing the chance of positive regulatory outcomes.

The FDA described its future work on the integrated assessment template as a continuous improvement cycle to ensure the needs of all stakeholders are addressed. Following the public workshop, FDA Docket No. FDA-2020-N-1550 was open until 30 December 2020 to accept additional public comment.⁵ The FDA plans to evaluate the docket comments received and hold a future public workshop to gather additional feedback from stakeholders to further refine the inclusion of information within the template.

Conclusion

From a regulatory affairs perspective, the details provided within the appendices will be of greatest importance, in contrast to other stakeholder groups that may benefit more from the more concise, consolidated summaries contained within the executive summary and interdisciplinary assessment portions of the template. As the reviewers from their respective disciplines determine which documentation to include within the appendices, it is anticipated that consideration for inclusion is given not only to information that is considered to be supportive, but also the information that was not considered supportive in order that future sponsors might potentially re-approach with improvements to enable the acceptance or avoid altogether. The term “appendices,” while sometimes connotated with being superfluous, might be more adequately termed a “roadmap,” leaving sponsors with directions to move forward, go in another direction, or plan to avoid. Increased transparency facilitated by the FDA helps enable increased predictability of regulatory success, which ultimately benefits a range of stakeholder groups, not least, the patient.

About the author

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References

1. Food and Drug Administration. Modernizing FDA's new drugs regulatory program. <https://www.fda.gov/drugs/regulatory-science-research-and-education/modernizing-fdas-new-drugs-regulatory-program>. Current as of 17 January 2020. Accessed 22 March 2021.
2. Food and Drug Administration. Federal Register website. New Drugs Regulatory Program modernization: Improving approval package documentation and communication. <https://www.federalregister.gov/documents/2019/06/27/2019-13751/new-drugs-regulatory-program-modernization-improving-approval-package-documentation-and>. Publication 27 June 2019. Accessed 22 March 2021.
3. Hearn-Stewart R. Implementation [FDA workshop presentation: Integrated assessment of marketing applications virtual workshop, slides 29-37.] <https://www.fda.gov/media/143534/download>. Presented 30 October 2020. Accessed 22 March 2021.
4. Lee KJ, Sager N. Rationale for development & core design features [FDA workshop presentation: Integrated assessment of marketing applications virtual workshop, slides 8-28.] <https://www.fda.gov/media/143534/download>. Presented 30 October 2020. Accessed 22 March 2021.
5. Food and Drug Administration. Regulations.com website. New Drugs Regulatory Program modernization: Implementation of the integrated assessment of marketing applications and integrated review documentation; public workshop; request for comments [Document ID: FDA-2020-N-1550-0001]. <https://www.regulations.gov/document/FDA-2020-N-1550-0001>. Posted 13 August 2020. Accessed 22 March 2021.