Maximizing the potential of the FDA assessment aid: Genentech’s experience

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Abstract  The assessment aid (AAid), an initiative of the US Food and Drug Administration’s (FDA’s) Oncology Center of Excellence (OCE), was introduced in 2018 as a pilot program to help streamline the agency’s review of oncology drug applications. In this article, Genentech shares its experience with the AAid to date and provides recommendations for preparing the AAid and improving the process to fully realize its benefits. Keywords — assessment aid, FDA OCE pilots, oncology drug review, Project Orbis, real-time oncology review

Background  The OCE developed the AAid to facilitate its assessment of new drug applications (NDA), biologic license applications (BLA), and supplemental applications. The AAid is based on the FDA multidisciplinary review template used by the agency to communicate the basis of drug approvals. Allowing the applicant to voluntarily populate the AAid with a summary and assessment of its own data frees up time the agency would otherwise be using to populate the
The main objective of the AAid is to focus the agency’s review on the most critical aspects of the dossier to increase review efficiency and consistency, and decrease review time spent on administrative tasks. The OCE has encouraged applicants to keep the document as scientific, factual, and technical as possible and without the inclusion of any promotional or interpretive language to mirror how the FDA approaches its review because the document is also used to fulfill FDA’s review requirements and satisfy its internal processes. This also helps reduce the need for the FDA to seek clarification from the applicant throughout the review. The AAid creates a streamlined review process by permitting FDA reviewers to focus on key results and perform critical analyses of the data. It is important to note that the AAid helps answer key regulatory questions more thoroughly and effectively.

The applicant should include only critical information that is relevant to the assessment of benefit-risk, as the entire document should be no longer than 100 pages for new molecular entities (NMEs) applications or 75 pages for supplemental applications. The AAid is a general template, and the applicant needs to provide information only in the sections relevant to the current submission. Once submitted, the applicant generally does not have the opportunity to revise its portion of the AAid; however, it is possible that the agency could request supplementary information during its review. Detailed instructions for completing the AAid are provided by the OCE in the AAid standard operating procedure (SOP) for the applicant and AAid instruction to the applicant.

If the applicant participates in the RTOR program, it may submit the AAid before, or at the time of, supplemental NDA/BLA submission. For non-RTOR, the AAid may be submitted within 30 days from the time of the supplemental NDA/BLA submission.

However, the agency encourages early submissions to facilitate the review process. Although participation in the AAid pilot is voluntary, in February 2020, the OCE communicated that the AAid was useful to the agency reviewers and recommended that Genentech submit AAids for all oncology filings. Given that additional time and resources are needed to prepare the AAid, Genentech has since then considered the AAid as a standard document in its oncology marketing applications to allow effective scheduling and planning for the AAid within the context of the broader dossier requirements to facilitate FDA’s review.
Genentech experience with the AAid
Since the start of the AAid pilot in 2018 and through September 2021, Genentech has completed 17 AAids for submissions across four of the five FDA oncology review divisions, within the following categories:

- 1 initial marketing authorization for a new molecular entity (AAid only)
- 16 supplemental license applications including:
  - 9 AAids only (ie, not as part of special review procedure)
  - 7 as part of RTOR
  - 6 as part of Project Orbis
  - 5 as part of RTOR and Project Orbis

In line with the OCE feedback, AAids for RTOR were submitted earlier than those for non-RTOR with respect to the time of supplemental NDA/BLA submission to facilitate the review process. The earliest AAid submission was 1 month before the final component submission (RTOR), and the latest was 3 months after the BLA submission (non-RTOR). Although the timeline for the AAid can be assessed and agreed with the agency on a case-by-case basis for RTOR submissions, there may be delays in review timelines if the AAid is gated on the availability of later documents, such as the clinical overview. Genentech included the AAid as a standard document in its oncology marketing applications in 2020, so the AAids for non-RTOR have been submitted at the time of supplemental NDA/BLA submission, although the agency is open to receiving the AAid up to 30 days after submission of the complete dossier.

Based on this experience, Genentech has established a number of key recommendations for preparing the AAid. In addition, it has identified several areas that could warrant greater clarity for criteria and processes to fully realize the benefits of the AAid.

Recommendations to sponsors preparing the AAid

Planning and communication

- Incorporate the additional timeline and resources needed to prepare the AAid into the overall submission plan. Although there may be additional considerations and shifting of resources, the benefit of more efficient reviews seems to offset most of these concerns.
- Perform detailed content mapping of the AAid ahead of data availability based on documents included in the dossier, as well as identifying which sections require de novo text and which tables require additional programming to streamline the critical path writing activities.
- Ensure early cross-functional alignment on data to be included in the AAid to save time and increase efficiency.
- Proactively engage in discussions with the FDA particularly when the data supporting an application is atypical. As an example, the AAid template currently has sections that are not applicable to applications focused on modeling or clinical pharmacology data. This will help ensure the AAid focuses on the most relevant review issues. One avenue to engage with the FDA is by using the briefing package and presubmission meeting for questions related to the AAid.
• Clearly define the roles and responsibilities within functions (e.g., authoring and reviewing) and set clear expectations for the review team, to encourage a “content check” approach, and discourage wordsmithing/revising text taken from dossier documents.

**Execution**

• Populate, review, and finalize data-independent portions ahead of data readout to save time once data become available.

• Directly re-use/adapt content that has already been developed and reviewed (e.g., CSR, protocol, module 2 summaries), including leveraging existing programmed tables, wherever possible, to save time and increase efficiency.

• Keep the page limit of the document in mind (100 pages for NMEs, 75 pages for supplemental applications) – concise editing and brevity of text is required to keep to the limits.

• Submit the AAid in Word format (in Module 1.11.3) because the FDA adds its assessments to the same document.

**Proposed process improvement**

Genentech has identified a number of areas for potential improvements, based on its experience to date:

• Establishment of a publicly available centralized location that houses the AAid template, SOP, and instructions to the applicant to ensure that the most recent versions of these documents are always available to the applicants.

• Inclusion of a version number, effective date, and summary of changes for new versions within the AAid template to allow applicants to focus on assessing the revisions and implementing any changes to internal processes.

• Receipt of the completed AAids once they have been finalized by the FDA reviewers would allow applicants the opportunity to better tailor the content of future AAids to meet the FDA’s needs. Genentech recognized challenges with sharing an unredacted version of the AAid but suggests that provision of additional mechanisms or venues, such as debriefs between the applicant and the FDA review team to understand how the FDA reviewers are using the AAid, would allow optimization of the content.

**Future of the AAid**

The use of the AAid can increase the review efficiency. As such, the FDA may seek to expand the scope of this pilot to include investigational new drug (IND) applications and nononcology products. Furthermore, there may be benefit to the adoption of this document by other health authorities to help harmonize global regulatory submissions, particularly for those health authorities participating in the Project Orbis pilot.
**Expansion to IND applications**

In June 2020, the OCE expressed interest in expanding its learnings from the AAids for license applications and initiated a pilot to streamline the internal review of oncology IND applications. This initiative is currently focused on the nonclinical/clinical review of INDs and may involve other functions (e.g., chemistry, manufacturing, and control) later on.

From September 2020 through April 2021, Genentech prepared AAids for IND applications and its experience to date indicates that most of the IND AAid content can be derived directly from the protocol, thus gating the AAid preparation to the protocol finalization. Premapping protocol section text to the table rows of the IND AAid is therefore highly recommended. One key challenge is to fit the required information to the word limits, especially for complex protocols or study designs. In addition, for some INDs, there is important protocol-specific information that the template does not accommodate.

In April 2021, the FDA paused the AAid pilot for INDs, with the OCE citing conflicts around internal FDA IND review systems and the AAid. However, should the AAid for IND pilot continue, Genentech proposes that the AAid could replace the summary documents prepared by applicants for an IND and that the AAid be submitted only for initial INDs—not administrative or cross-referenced INDs. Furthermore, consideration should be given to any crucial aspects of study design not covered elsewhere in the AAid template, to be placed in the "Other important design issues" section, to ensure the FDA can focus on the critical review aspects. Increased clarity on the specific requirements for each section would facilitate this. Genentech also proposes that the selected protocol elements in the AAid align as much as possible with ICH E6(R2) protocol elements to assist applicants in completing the AAid for INDs. If successful, this pilot could expedite the agency’s review of future INDs.

**Expansion and harmonization across FDA review divisions**

The AAid is an OCE pilot and currently submitted only with applications for oncology products. In 2020, the FDA’s Center for Drug Evaluation and Research began to introduce the outcomes of its initiative to modernize the New Drugs Regulatory Program, including the integrated assessment review process and documentation template. This template aims to more clearly communicate FDA’s analysis of the scientific issues raised by the application and communicate the basis for the regulatory decision more effectively. From a sponsor’s perspective, it would be interesting to see how the integrated assessment template impacts the OCE’s AAid template and whether the principle of the sponsor populating data sections to make the agency’s review more efficient are to be extended beyond applications for oncology products.

**Advancing global harmonization of regulatory submissions**

Another benefit of the AAid is its ability to serve as a shared document facilitating parallel review and guiding discussions between the FDA and regulatory agencies outside the US participating in Project Orbis. This ensures consistency in the basis for approvals from international health authorities through this pilot. As the use of the AAid becomes more routine for licensing
applications in the US under Project Orbis, it would be beneficial to have further
guidance on the content of the AAid that would allow a more streamlined and
harmonized international review, especially as Genentech has already received
a request from a health authority outside of the US to include the AAid with its
applications. It may also be beneficial to use the AAid as an interactive tool in
the future to exchange information with the FDA and other health authorities to
allow applicants to share information in real-time to further expedite drug
product reviews and ultimately, global patient access to medicines.
Furthermore, ongoing initiatives such as the development of a cloud-based
submission platform could facilitate a more targeted content-based (rather
than document-based) interactive review of the assessment aid.

Conclusion
Since the start of the AAid pilot in 2018, the use of the AAid is becoming more
common for oncology licensing applications in the US and its benefits are even
being realized by other health authorities around the globe. As both the FDA
and applicants are gaining more experience with each submission, continued
dialogue between the agency and industry is critical to further refining the
requirements and processes as well as expanding the scope to maximize the
potential and fully realize the benefits of the AAid.

Abbreviations
AAid, assessment aid; BLA, biologic license application; CMC, Chemistry, manufacturing, and
controls; FDA, [US] Food and Drug Administration; IND, investigational new drug; NDA, new drug
application; NME, new molecular entity; OCE, Oncology Center of Excellence; RTOR, real-time
oncology review [program]; SOP, standard operating procedure.

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References
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