Real-Time Oncology Review (RTOR)
Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (OCE) R. Angelo De Claro at 301-796-4415 or (CBER) Office of Communication, Outreach and Development at 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

July 2022
Administrative/Procedural

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to provide recommendations to applicants on the process for submission of selected New Drug Applications (NDA) and Biologic License Applications (BLA) with oncology indications for review under the Real-Time Oncology Review (RTOR).[2]

This guidance does not address FDA's expedited programs such as the Fast Track Designation, Breakthrough Therapy Designation, or Priority Review Designation. Additional information on these expedited programs can be found in the *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics*.[3]

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

The FDA Oncology Center of Excellence (OCE), in collaboration with the Office of Oncologic Diseases (OOD), commenced the RTOR program in February 2018 to facilitate earlier submission of top-line results (i.e., efficacy and safety results from clinical studies before the

[1] This guidance has been prepared by the Oncology Center of Excellence in consultation with the Office of Oncologic Diseases in the Center for Drug Evaluation and Research (CDER), and Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] Real-Time Oncology Review Program: https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program.

[3] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

study report is completed) and datasets, after database lock, to support an earlier start to the FDA application review.[4] Initially, only supplemental oncology drug[5] applications (to add new indications, dosing regimens, or other clinical information to the prescribing information) were reviewed under RTOR. Later the program was expanded to include select original oncology NDAs for new molecular entities (NMEs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act and original oncology BLAs submitted under section 351(a) of the Public Health Service Act.

In a typical FDA drug review process, efficacy and safety data are submitted at the same time as other elements of a drug application (e.g., administrative information, summary documents, clinical study reports, manufacturing information, and nonclinical study reports, etc.) for a complete application. However, the process of assembling a drug application for submission usually takes at least several months. The OCE developed RTOR to facilitate earlier submission of critical efficacy and safety data to initiate FDA's evaluation of the application, whereby components of individual modules (e.g., parts of the clinical module, etc.) may be submitted at separate times. RTOR is different than the existing mechanisms for rolling review in which, generally, complete modules (e.g., the complete clinical module) are submitted prior to a complete application submission. The intent of RTOR is to provide FDA reviewers earlier access to data, to identify data quality and potential review issues, and potentially provide early feedback to the applicant, which can allow for a more streamlined and efficient review process.

RTOR does not alter the review performance goals and timelines associated with the applications, including as described in the Prescription Drug User Fee Amendments (PDUFA). Although early approvals have occurred with applications included in the RTOR, this may not be feasible for all applications due to specific issues that may be identified with the application or overall workload considerations. Acceptance into the RTOR program does not guarantee or influence approval of the application, which is subject to the same statutory and regulatory requirements for approval as applications that are not included in RTOR. Participation by the applicant in this program is voluntary. If at any point FDA determines participation in the program is no longer appropriate, FDA may rescind acceptance and instruct the applicant to use routine submission procedures for their application.

III. ELIGIBLE APPLICATIONS

To be considered for RTOR, submissions should demonstrate the following:

[4] U.S. Food and Drug Administration: Initial Experience with the Real-Time Oncology Review Program. R. Angelo de Claro, et al. *Clin Cancer Res* August 19 2020: https://clincancerres.aacrjournals.org/content/early/2020/08/19/1078-0432.CCR-20-2220.

[5] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

- Drug is likely to demonstrate substantial improvement over available therapy or to qualify[6] for FDA's Expedited Programs[7]

- Straightforward study designs as determined by the review division and the OCE

- Easily interpreted clinical trial endpoints (e.g., overall survival, response rates), as determined by the review division and OCE

RTOR involves early engagement with the applicant to discuss the submission timelines for RTOR components and the full application submission. To initiate an RTOR submission, FDA would need the top-line efficacy and safety results from the pivotal clinical trial(s). At this stage, the applicant should have already completed the database lock for the clinical trial. RTOR is not designed to receive live updates of clinical trial data.

IV. RTOR PROCESS

- At the time top-line results of a pivotal trial(s) are available and the database has been locked, an applicant may apply for review under RTOR by submitting a request via email to their assigned Regulatory Project Manager (RPM) and to the Investigational New Drug Application (IND). The applicant should include their top-line results and a written justification explaining how their application demonstrates that it is appropriate for RTOR, as described in Section III above. The applicant should also include a proposed timeline of when it will submit the various components of the RTOR application (listed below). The review division director/deputy director, with input from the review team (including reviewers, team leaders, and management from all relevant review disciplines), will decide whether the application will be selected for the RTOR program. This decision will generally be made within 20 business days of receipt of the request and communicated to the applicant via email.

- If the application is not accepted into the RTOR program, the applicant should follow routine application submission procedures.

- Once an application is selected, a teleconference with the applicant may be scheduled if necessary (generally within 20 business days). The OOD clinical division director/deputy director, the review team, and OCE staff may participate in this meeting. FDA and the applicant will discuss the plan for RTOR and reach tentative agreement on proposed submission timelines for the drug application.

[6] RTOR may not be suitable for certain biological products, such as cell and gene therapies, for which complex manufacturing and product characteristics need to be considered in evaluating the safety and efficacy of the product. For these types of products, we recommend that a discussion of whether the product is suitable for RTOR take place with the appropriate review division.

[7] See the guidance for industry: *Expedited Programs for Serious Conditions – Drugs and Biologics* (May 2014).

- The applicant should submit the following items to their marketing application per the agreed-upon timeline:

    - Top-line efficacy/safety tables/figures

    - Complete Study Data Tabulation Model (SDTM)[8] dataset package

    - Complete Analysis Data Model (ADaM) datasets for key efficacy and safety tables/figures for pivotal study (see OOD data specifications[9] for requested format of safety datasets)

    - The protocol and amendments (a list of major changes for each amendment), Statistical Analysis Plan (SAP), and Data Monitoring Committee (DMC) charter and DMC minutes

    - Statistical (e.g., SAS) programs

    - Proposed labeling

    - Summary of data and rationale supporting dose and dosing regimen selection (including key population pharmacokinetics (PK), physiologically-based (PB)/PK and exposure-response reports, analyses programs, and datasets)

    - Summary of clinical pharmacology studies and datasets supporting the conclusions

    - Key results, analysis, and datasets for other disciplines (e.g., clinical pharmacology), if applicable

    - Final study reports of all supportive studies, including pharmacology and toxicology studies

    - Case report forms (CRFs) as required by applicable regulations[10]

    - All Chemistry, Manufacturing, and Controls (CMC) information, if appropriate, including list of all manufacturing, testing and critical intermediate facilities with addresses and FDA Establishment Identifier (FEI) numbers other than stability data for registration batches (if not available) for drug substance(s) and drug product

[8] FDA Study Data Standards Resources: https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources.

[9] OOD Data Specifications: https://www.fda.gov/media/133252/download.

[10] See 21 CFR 314.50.

- Pediatric study plan (as required)
- Request for proprietary name review (as required)
- Final clinical study report(s)

- In general, FDA recommends bundling these items into a maximum of three partial submissions and a final submission.

- During the pre-NDA/BLA meeting[11] to discuss the proposed application, FDA may share preliminary key review questions or issues and critical analyses needed. If FDA requests additional analyses, the applicant may submit them before or at the time of submission of the complete marketing application. In some cases, if FDA agrees, the applicant may submit the requested additional analyses after the marketing application is submitted. These discussions may be documented in the meeting minutes under the section, "Agreement of a Complete Application" for NDA NMEs or original 351(a) BLAs. For supplemental applications, RPMs may capture agreements discussed under "Additional Items Discussed" or under discussion of specific questions as appropriate in the official meeting minutes.

- The applicant submits the final component of the marketing application. Once FDA receives the final component the application is considered complete, and the review clock will start. The complete application will include any remaining components not previously submitted by the applicant.

V. ADDITIONAL REGULATORY CONSIDERATIONS

As noted above, the applicant should send RTOR items listed in Section IV as partial submissions to the NDA or 351(a) BLA. Within the cover letter of the partial submission, the subject line should be identified as: "**PARTIAL SUBMISSION FOR [INSERT INDICATION] [CHOOSE: ORIGINAL APPLICATION OR EFFICACY SUPPLEMENT] WITH [INSERT TYPE OF INFORMATION SUBMITTED, e.g., CLINICAL/STATISTICS] INFORMATION FOR REAL-TIME ONCOLOGY REVIEW (RTOR)**." In Box 21 of Form FDA 356h, the applicant should identify the submission as original or efficacy supplement and in Box 22, the applicant should indicate that the RTOR components are a partial submission toward submission of the complete application. An updated Reviewer's Guide should be submitted with each submission.[12]

[11] See the draft guidance for industry: *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (December 2017). When final, this guidance will represent the FDA's current thinking on this topic.

[12] See the technical specifications document: *eCTD Technical Conformance Guide* (December 2019).

Where an application fee is required for the NDA or BLA under PDUFA, the fee must be submitted when the first component of the RTOR is submitted to the marketing application.[13]

[13] Sec. 736(a)(2), 736(e).