
Real-Time Oncology Review (RTOR) Guidance for Industry

**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)**

**November 2023
Administrative/Procedural**

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*Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
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Phone: 800-835-4709 or 240-402-8010
Email: ocod@fda.hhs.gov*

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This guidance represents 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 (NDAs) and biologics license applications (BLAs) with oncology indications for review under 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* (May 2014).³ RTOR is separate from the Split Time Application Review (STAR) pilot program which was established under the Prescription Drug User Fee Act (PDUFA) VII commitments.⁴

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and 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.

¹ This guidance has been prepared by the Oncology Center of Excellence (OCE) 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>.

⁴ Split Real Time Application Review: <https://www.fda.gov/drugs/development-resources/split-real-time-application-review-star>.

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II. BACKGROUND

The FDA Oncology Center of Excellence (OCE), in collaboration with the Office of Oncologic Diseases (OOD), commenced RTOR in February 2018 to facilitate earlier submission of top-line results (i.e., efficacy and safety results from clinical studies before the study report is completed) and datasets, after database lock, to support an earlier start to the FDA application review.⁵ Initially, only supplemental oncology drug⁶ applications (to add new indications, dosing regimens, or other clinical information to the prescribing information) were reviewed under RTOR. The program was expanded later 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 from the existing mechanisms for submission of portions of an application 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 to potentially enable 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 PDUFA. Although early approvals have occurred with applications included in 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 RTOR 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:

⁵ de Claro, RA, JJ Gao, T Kim, PG Kluetz, MR Theoret, JA Beaver, R Pazdur, 2021, U.S. Food and Drug Administration: Initial Experience with the Real-Time Oncology Review Program, *Clin Cancer Res*, 27 (1): 11-14.

⁶ For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

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- Clinical evidence from adequate and well-controlled investigation(s) indicates that the drug may demonstrate substantial improvement on a clinically relevant endpoint(s) over available therapies.⁷
- Easily interpreted clinical trial endpoints (e.g., overall survival, response rates), as determined by the review division and OCE.
- No aspect of the submission is likely to require a longer review time (e.g., requirement for new REMS, advisory committee, etc.).

RTOR involves early engagement with the applicant to discuss the submission timelines for RTOR components and the full application submission. To determine eligibility for RTOR, 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.

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 to the Investigational New Drug Application (IND). The applicant should include their top-line results and submit RTOR Request information⁸, which includes information such as the justification explaining how their application demonstrates that it is appropriate for RTOR, as described in Section III above and 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 RTOR. 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 RTOR, 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.

⁷ 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.

⁸ Applicants should contact their assigned Regulatory Project Manager (RPM) for information that should be submitted in an RTOR request.

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- The applicant should submit the following items to their marketing application per the agreed-upon timeline:⁹
 - Top-line efficacy/safety tables/figures
 - Complete Study Data Tabulation Model (SDTM)¹⁰ dataset package
 - Complete Analysis Data Model (ADaM) datasets for key efficacy and safety tables/figures for pivotal study (see OOD data specifications¹¹ 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 regulations¹²
 - 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

⁹ For an example RTOR submission timeline, refer to the RTOR website at <https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program>.

¹⁰ FDA Study Data Standards Resources: <https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources>.

¹¹ OOD Data Specifications: <https://www.fda.gov/media/133252/download>.

¹² See 21 CFR 314.50.

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data for registration batches (if not available) for drug substance(s) and drug product

- Pediatric study plan (as required)
 - Request for proprietary name review (as required)
 - Final clinical study report(s)
 - Bioresearch monitoring (BIMO) information (as applicable)¹³
 - Other documents as necessary, e.g., for Modules 1, 2, 4, and 5
- In general, FDA recommends submitting these items in a maximum of three presubmissions and a final submission.
 - During the pre-NDA/BLA meeting¹⁴ 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.
 - When FDA receives the final component, the application is considered complete, and the review clock will start.

V. ADDITIONAL REGULATORY CONSIDERATIONS

As noted above, the applicant should submit RTOR items listed in Section IV as presubmissions to the NDA or 351(a) BLA. Within the cover letter of the presubmission, the subject line should be identified as: **“PRESUBMISSION 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

¹³ For the content and format of this information, see the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018). When final, this guidance will represent the FDA’s current thinking on this topic.

¹⁴ See the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (September 2023). When final, this guidance will represent the FDA’s current thinking on this topic.

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should identify the submission as original or efficacy supplement and in Box 22, the applicant should indicate that the RTOR components are a presubmission. When the last component is submitted, the applicant should identify that the application is complete. An updated Reviewer's Guide should be submitted with each submission.¹⁵

Where an application fee is required for the NDA or BLA under PDUFA, the fee must be submitted when the first component of RTOR is submitted to the marketing application.¹⁶

¹⁵ See the technical specifications document: *eCTD Technical Conformance Guide* (November 2022).

¹⁶ Sec. 736(a)(1), 736(e) of the Federal Food, Drug, and Cosmetic Act.