PINK SHEET
CITELINE REGULATORY

09 Nov 2023 | **Analysis**

Real-Time Oncology Review Excludes Applications Needing Adcomms Or New REMS

by Sue Sutter

Applications no longer need to have 'straightforward study designs' to qualify for RTOR, but no aspect of the submission should be likely to require a longer review time, US FDA says in a final guidance on the expedited pathway.

Only relatively uncomplicated drug or biologic applications that can be quickly reviewed are suitable for the US Food and Drug Administration's Real-Time Oncology Review program, the agency clarifies in a guidance on the expedited pathway.

To be considered for RTOR, "no aspect of the submission is likely to require a longer review time," such as for a new Risk Evaluation and Mitigation Strategy or an advisory committee, the agency says in a final *guidance* announced on 7 November.

This condition is one of three criteria that applications must satisfy to qualify for RTOR. It replaces a draft guidance requirement for "straightforward study designs as determined by the review division" and the Oncology Center of Excellence.

Elimination of this requirement may have been in response to industry comments on the July 2022 draft guidance. In separate comments, *Pfizer Inc.* and the Alliance for Regenerative Medicine said it would be helpful if the agency could provide a clearer definition of what constitutes a straightforward study design or examples of such designs.

As with the draft, the final guidance lists two other RTOR qualifying criteria.

The draft included a requirement that the drug "is likely to demonstrate substantial improvement over available therapy or to qualify for FDA's Expedited Programs." The final

guidance brings more specificity to this requirement, stating: “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.”

The third qualifying criterion is unchanged from the draft: “Easily interpreted clinical trial endpoints (e.g., overall survival, response rates), as determined by the review division and OCE.”

Overall, the final guidance is little changed from the draft document, save for what the FDA describes as clarifications of terminology and the submission process, and changes to align the guidance with the RTOR website. (Also see "*US FDA’s Real-Time Oncology Review Program Is No Guarantee For Early Approval*" - Pink Sheet, 27 Jul, 2022.)

It Started With Supplements

OCE and the Office of Oncologic Diseases introduced RTOR in February 2018 to facilitate earlier submission of top-line results, such as efficacy and safety results from clinical trials before the study report is completed, and datasets to support an earlier start to the FDA’s application review. (Also see "*Gottlieb Uses ASCO Platform To Unveil Two Pilot Programs To Speed Drug Review*" - Pink Sheet, 3 Jun, 2018.)

The program initially was limited to supplemental applications but subsequently expanded to original new drug applications and biologics license applications for oncology agents.

The program has been effective and popular. A total of 74 applications have been approved under RTOR to date, with approximately one-fourth of the approvals for original NDAs and BLAs, according to FDA data. The *Pink Sheet* *Performance Tracker* lists six applications pending under RTOR.

An August 2022 *Pink Sheet* analysis found that RTOR shaved a median of 1.5 months from the review timeframes for supplemental applications and one month from originals. (Also see "*US FDA’s RTOR Program Produces Approvals About One Month Sooner Than Priority Review Goal*" - Pink Sheet, 5 Aug, 2022.)

Story continues after chart ...

Click here to explore this interactive content online

As in the draft guidance, the final document continues to caution that RTOR may not be suitable for certain biological products, such as cell and gene therapies, which involve consideration of complex manufacturing and product characteristics.

PINK SHEET
CITELINE REGULATORY

Center for Biologics Evaluation and Research Director Peter Marks has said a new pilot program for rare diseases seeks to leverage the basic philosophy of RTOR, reducing the amount of time between trial completion and agency vetting of the results. (Also see "*US FDA Eyes Project Orbis-Type Approach For Cell And Gene Therapies*" - Pink Sheet, 13 Feb, 2023.)

The recently launched CBER pilot, known as Support for clinical Trials Advancing Rare disease Therapeutics (START), is aimed at bringing the same types of extensive interactions and intensive communications that characterized the development of COVID-19 vaccines under Operation Warp Speed to the development of cell and gene therapies for rare diseases. (Also see "*Pilot Phase Of Operation Warp Speed For Rare Diseases Beginning Soon*" - Pink Sheet, 20 Sep, 2023.)

Aligning Criteria With STAR

RTOR's success also led to the creation, through the seventh iteration of the Prescription Drug User Fee Act, of the Split Real-Time Application Review (STAR) program, which aims to shorten the time from complete submission to action date to enable earlier patient access to therapies that address an unmet need. The STAR pilot program applies to efficacy supplements across all therapeutic areas and review disciplines that meet specific criteria. (Also see "*US FDA Begins Implementing New User Fee Programs, But What About The Actual Fees?*" - Pink Sheet, 4 Oct, 2022.)

The RTOR eligibility criteria in the final guidance mirror two of the STAR eligibility criteria: clinical evidence from adequate and well-controlled studies indicates the drug may demonstrate substantial improvement on a clinically relevant endpoint, and no aspect of the submission is likely to require a longer review time, such as for a new REMS.

There are two additional STAR criteria:

- The application is for a drug intended to treat a serious condition with an unmet medical need; and

- There is no chemistry, manufacturing or control information that would require a foreign manufacturing site inspection (i.e., domestic site inspections may be allowed if it does not affect the expedited timeframe).

The RTOR final guidance clarifies that the oncology expedited program is separate from the STAR pilot.

As with the RTOR draft guidance, the final guidance includes a list of items that should be submitted to a marketing application pursuant to a timeline agreed upon with the FDA. The final guidance includes two new additions in this category: bioresearch monitoring information, as

applicable, and "other documents as necessary, e.g., for Modules 1, 2, 4 and 5."

The FDA generally recommends submitting these items in a maximum of three presubmissions and a final submission. The term presubmission is new in the final guidance; these early submissions were referred to as partial submissions in the draft guidance.