Paper SA01

Real Time Oncology Review – Applicant Experience

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ABSTRACT

The Food and Drug Administration (FDA) Oncology Center of Excellence Real-Time Oncology Review (RTOR) pilot program aims to explore a more efficient review process to ensure that safe and effective treatments are available to patients as early as possible, while maintaining and improving review quality and balancing the review team's workload through data and analysis standardization, and early iterative engagement with the applicant. At the time of top-line results of a pivotal trial, if certain eligibility criteria are met, an applicant can apply for the RTOR pilot by notifying the appropriate division Regulatory Project Manager.

Janssen applied for this pilot program for 2 supplemental filings in 2019. This paper covers our experience participating in this program. We also cover the recommended timeframe for FDA interactions and provision of submission components and specific examples of how such deliverables were completed for the representative submissions.

INTRODUCTION

RTOR differs from other accelerated submission approaches such as rolling submissions as topline results and datasets to support key analysis are submitted to the agency in advance of the underlying study reports being finalized, which enables the agency to get a head start on the review process.

The Janssen teams addressed complexities on submission of a partial electronic submission dataset package for the key analysis first as the RTOR early package, followed by remaining datasets to support other non-key analysis along with the study reports. These challenges were addressed both from a statistics and programming operational process perspective as well as regulatory submission management and publishing perspective.

Cross functional teams had to understand the impact of analysis updates after the submission of the RTOR early package datasets, evaluate the impact on the information already submitted and agree on an approach to resubmit certain updated information to the FDA as needed. This led to early and robust definition of adhoc analyses and an early issuance and submission of approved study reports to the FDA in advance of the filing.

Early engagement with FDA reviewers enabled Janssen to conduct additional analysis deemed important from a reviewer's perspective by responding to FDA Information Requests (IRs) in advance of supplemental filing. This facilitated robust and focused discussions during teleconferences and application orientation meetings with the FDA early in the review process, leading to an efficient and expedited review.

CURRENT REGULATORY MECHANISMS FOR ENHANCED AND EXPEDITED ENGAGEMENT WITH REVIEW TEAM

RTOR is one of many regulatory mechanisms available for early engagement with the application review team at the FDA[1]. Some examples of these include;

- Accelerated approval; Conditional approval is granted using surrogate endpoints or intermediate clinical endpoints. Additional results from controlled trials with hard clinical endpoints are required to confirm clinical benefit.
- Priority review; Action on an application within 6 months, compared to 10 months under standard review.
- Fast track; Rolling submission of completed sections of the (s)NDA / (s)BLA. Eligible for priority review if criteria are met.
- Break through therapy designation; Supports an abbreviated development plan (e.g.: Accelerated approval standard) with frequent agency interactions and guidance on development program. Eligible for fast track and thereby priority review if criteria are met.

RTOR[2] is a pilot program and an Initiative by the Oncology Center of Excellence which works with Center for Drug Evaluation and Research / Center for Drug Biologics and Research / Office of Hematology and Oncology Products / Center for Devices and Radiological Health (CDER/CBER/OHOP/CDRH). The purpose of the pilot is multi-pronged and includes;

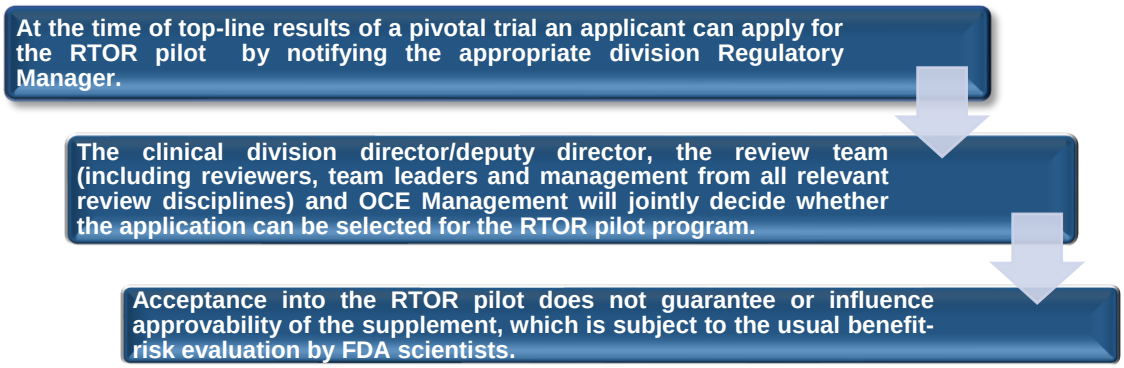
- Ensure Safe, Effective Treatments available to patients as early as possible
- Improve Review Efficiency
- Maintain/Improve Review Quality
- Balance Reviewer's Workload
- Early Iterative engagement with applicant

REAL-TIME ONCOLOGY REVIEW

Supplemental New Drug Application (sNDA) and Supplemental Biologic License Application (sBLA) submissions are within the scope of RTOR for drugs that are likely to demonstrate substantial improvements over available therapy, which may include drugs previously granted Breakthrough Therapy Designation for the same or other indications. Drugs meeting other criteria for other expedited programs (e.g. fast track, priority review) may also be considered. Additional criteria for candidates include Straight forward study designs, as determined by the review division and the OCE and studies with endpoints that can be easily interpreted (for example, overall survival in a randomized trial). Out of scope for RTOR are supplements with Chemistry, Manufacturing and Control (CMC) formulation changes and supplements with pharmacology or toxicology data, submissions with greater complexity, including those with companion diagnostics and studies conducted exclusively outside the United States and adjuvant, neoadjuvant, and prevention studies.

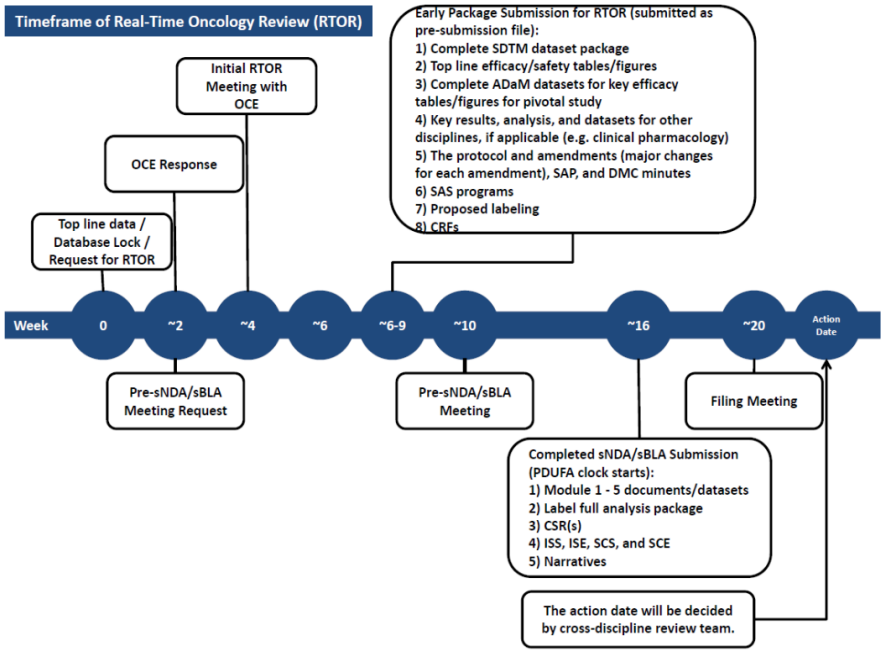
APPLICATION PROCESS

Application for RTOR follows the availability of top-line results of the pivotal trial and involves the following steps.



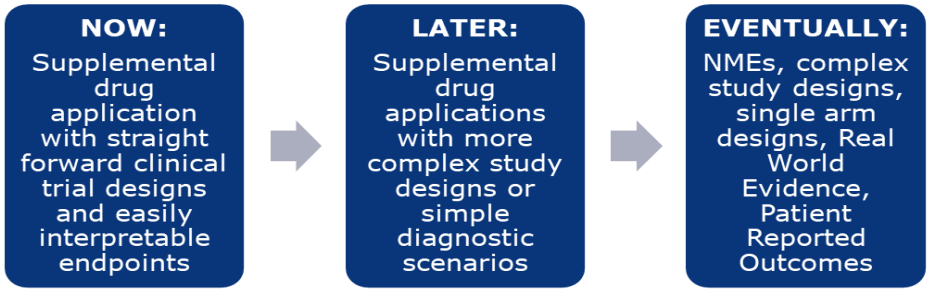
TIMEFRAME

The timeframe for RTOR package submission and review starts with the availability of topline data and request for participation in the RTOR pilot. The early package submission is around 6-9 weeks from the availability of topline data with the completed sNDA / sBLA submission at 16 weeks. Detailed timeframe for submission and planned interactions with the review team is as outlined below.



POTENTIAL FUTURE EXPANSION

Potential expansion of the pilot would be in a stepwise approach[3]. Current pilot only includes straightforward supplemental applications. Expansion would first move to more complex supplemental applications, then simple New Molecular Entities (NMEs)



APPLICANT EXPERIENCE

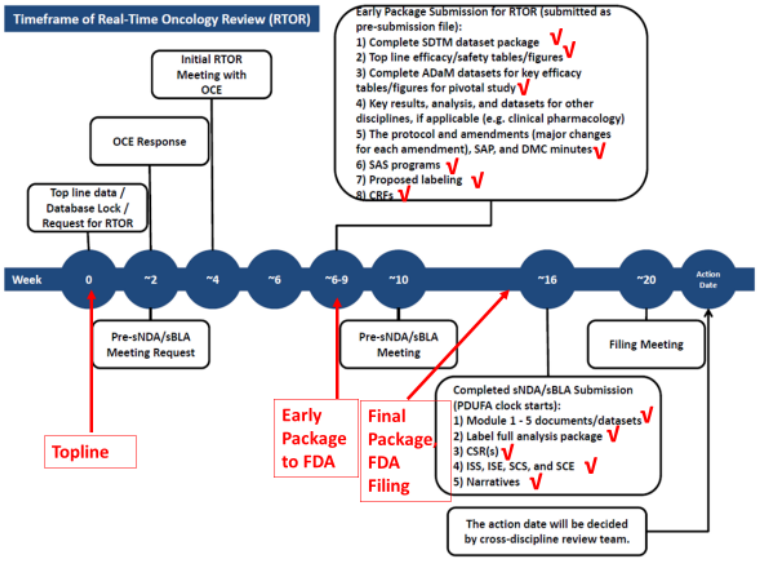
Key takeaways from early participants in the RTOR pilot as summarized in a white paper[3] were;

- Early engagement and clear communication with FDA on what type of information is needed and when is key
- Earlier submission of the following may help facilitate FDA review; General information/comments related to data derivation (i.e. grouped terms provided in draft US Prescribing Information (USPI)); Documentation to accompany datasets; Data definition files
- Information Requests (IRs) should be expected after submission of the "Pre-Submission Package". Quick response/submission is expected. Team should be prepared to be simultaneously working on deliverables for the "Full Dossier Submission" and IRs

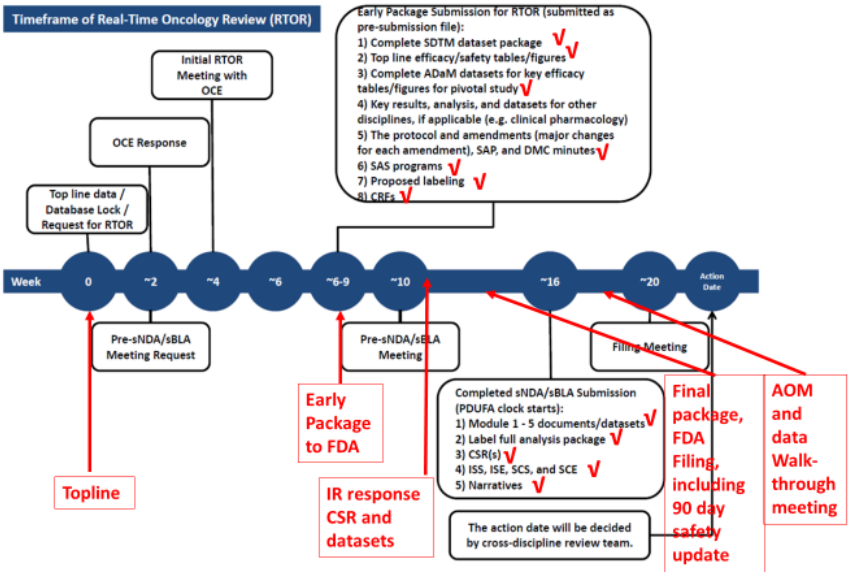
Our experience on the 2019 RTOR supplemental filings supported these takeaways. The lessons learned and some recommended best practices are outlined next.

TIMEFRAME FOR REPRESENTATIVE SUBMISSIONS

FIRST SUBMISSION:



SECOND SUBMISSION:



LESSONS LEARNED AND RECOMMENDED BEST PRACTICES

EARLY PLANNING OF SUBMISSION DATASETS AND DOCUMENTATION

Create submission compliant datasets and documentation upfront rather than after finalization of submission documents to ensure availability at the time of the RTOR early package submission. Applicant submitted complete data package and documentation (define.xml/pdf and adrg.pdf) instead of just Tables, listings and graphs or Analysis data without documentation for the RTOR early package. Key efficacy analysis datasets and complete SDTM was provided per pilot guidance in the RTOR early package. The complete analysis dataset package was later submitted at filing.

MINIMIZE RE-SUBMISSION OF DATASETS

Considering that there are multiple sequential dataset deliverables submitted to the agency, there is potential for changes to be made to the datasets if analysis is not finalized in an expedited manner. Such changes that would necessitate re-submission of earlier submitted datasets should be minimized as far as possible.

With datasets submitted via different sequences as part of RTOR early package, final package and IR responses, agency reviewers may have difficulty finding the correct location for these datasets in the Electronic Common Technical Document (eCTD) if viewed by submission sequence. As all datasets are not submitted in one package, this might lead to some confusion regarding the availability of all analysis datasets for the study.

As such, a recommendation is that when necessary only submit new or updated datasets and documentation in the final package.

EXPEDITE COMPLETION OF CSR

A stable approval draft of the Clinical Study Report (CSR) available by the time of RTOR early package delivery, enables finalization of the datasets to be sent as part of the RTOR early package. Cross functional teams have to understand the impact of analysis updates after submission of the RTOR early package datasets and to minimize these, early and robust definition, programming and interpretation of adhoc analyses is required.

For a referenced submission, CSR was finalized shortly after RTOR early package delivery which allowed for submission of the complete analysis dataset package along with the CSR in response to agency Information request (IR) between early and final package submission.

SYNCHRONOUS RESPONSE TEAM ALONGSIDE CORE SUBMISSION TEAM

Establishing a Response Team alongside the core Submission Team enables management of IR responses concurrent with submission document finalization. Regularly scheduled meetings with FDA to discuss RTOR package findings and questions routinely lead to IRs contemporaneous with final submission package preparation.

Biweekly teleconferences (agenda driven) + Face to Face Application orientation meetings and data walkthrough, provide opportunities for robust and focused discussions with review team given their familiarity with the data submitted earlier as part of the submission documents and datasets as well as IR responses within the RTOR period.

CONCLUSION

RTOR differs from other accelerated submission approaches as topline results and datasets to support key analysis are submitted to the agency prior to corresponding study reports.
Considerations on dataset submission need to be addressed both from a statistics and programming operational process perspective as well as regulatory submission management and publishing perspective.
RTOR Enables early engagement with FDA where FDA reviewers were able to review the data for completeness, send IRs for clarifications and additional analysis and the sponsor was able to respond to these in advance of sNDA filing. It provides an opportunity to address any data quality and potential review issues early on, enables early feedback regarding the most effective way to analyze data to properly address key regulatory questions and supports early scheduling of application orientation meeting and a more robust and focused discussion having given the review team's sound understanding of the submission components early in the review period.

REFERENCES

1 https://www.fda.gov/patients/learn-about-drug-and-device-approvals/fast-track-breakthrough-therapy-accelerated-approval-priority-review retrieved Sep 10 2019
2 https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program retrieved Sep 10 2019
3 [3]Friends of Cancer Research. (2018). Real-Time Oncology Review and the Assessment Aid: Increase Review Efficiency Through Standardization and Earlier Data Access [White paper] Retrieved Nov 20, 2018, from Friends of Cancer Research: https://www.focr.org/sites/default/files/pdf/ROTR%20White%20Paper%201.pdf

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