Paper SA04

Submission Experience with Real-Time Oncology Review, Project Orbis, and Priority Review

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ABSTRACT

The Food and Drug Administration (FDA) has many regulatory mechanisms available for early engagement with the application review team. In particular, the Oncology Center of Excellence (OCE) Real-Time Oncology Review (RTOR) program facilitates earlier submission of topline efficacy and safety results prior to the complete submission and supports an earlier start to the FDA's evaluation of the application. Project Orbis, initiated by the FDA OCE in May 2019, also provides a framework for concurrent submission and review of oncology products among international partners. It aims to give patients faster access to promising cancer treatments across the globe through collaboration among international regulatory agencies. Bayer applied for the RTOR program and Project Orbis for supplemental filings of Darolutamide in 2021 (ARASENS study). This paper covers our experience participating in the RTOR program, Project Orbis, and priority review through final approval from FDA. We also cover lessons learned and recommendations from our global submission activities.

INTRODUCTION

FDA Oncology Center of Excellence (OCE) launched multiple initiatives for achieving patient-centered regulatory decision-making through innovation and collaboration. Real-Time Oncology Review (RTOR) pilot program launched in February 2018 and Project Orbis launched in May 2019 are two of these initiatives. RTOR program provides the opportunity of earlier submission of topline efficacy and safety results for FDA's review before the complete submission package. Project Orbis provides a global collaborative review framework between FDA and international regulatory partners. The two can be integrated together for an efficient and streamlined submission and review process. Both mechanisms help bring the promising oncology treatments available to patients globally faster.

Bayer applied for the RTOR program and Project Orbis for supplemental filings of Darolutamide in December 2021 (ARASENS study) and got accepted in early January 2022. We received FDA approval 1 month ahead of the Prescription Drug User Fee Act (PDUFA) priority review timeline. By the time of the release of this paper, we received 5 approvals out of 7 Project Orbis Partners (POPs), and most approvals are earlier than standard review timelines. The team addressed the challenges for submission of the complete ADaM data package in the RTOR early package, compact global submission timelines, and intense information requests (IRs) from multiple health authorities (HAs) with overlapping timelines and short turnaround times. The collaboration between different functional groups, frontloading statistical and programming activities, extensive analytical and reporting standardization, and robust macro systems at Bayer all played key roles in our success.

This paper summarizes our experience of sNDA submission with RTOR, Project Orbis, and FDA priority review. We will start with an overview and brief introduction of RTOR and Project Orbis, followed by details of our submission experience under RTOR, FDA priority review and Project Orbis. In general, our submission experience aligns with the guidance and initial experiences shared in [1], [2], [3], [4]. Some lessons learned and recommendations will also be covered in the later sections.

REAL-TIME ONCOLOGY REVIEW

FDA Oncology Center of Excellence (OCE) launched Real-Time Oncology Review (RTOR) pilot program in February 2018. Different from the typical FDA submission and review process, in which efficacy and safety data are submitted together with other elements in the complete drug application submission, RTOR requests early submission of the key efficacy and safety data and results to FDA for the agency to start review early. The initial scope of RTOR is supplemental New Drug Applications (sNDAs) and supplemental Biologics License Applications (sBLAs) for oncology indications. It has been expanded now for New Drug Applications (NDAs) for new molecular entities (NMEs), original Biologics License Applications (BLAs), and sNDAs and sBLAs for oncology drug. To apply for RTOR, submissions need to meet criteria, such as for drugs likely to demonstrate substantial improvements over available therapy or qualified for Expedited Programs (e.g., fast track, priority review) within FDA. The study design should be straightforward with endpoints that can be easily interpreted (e.g., overall survival, response rates, etc.). At the time of topline results (TLR) of a pivotal trial are available, applicants can apply for the RTOR program by contacting the designated application regulatory project manager (RPM). The applicant will be notified about the decision on the acceptance of the RTOR program. Once approved, applicants and FDA will discuss the submission timelines for each RTOR component as well as the full application. Under the RTOR program, applicants are expected to bundle and submit all the application components as soon as they become available. All should be included in up to three pre-submission packages and a final submission. Proposed by general RTOR timelines in [1], the reference start week (Week 0) can be defined by database lock/TLR available/RTOR request. The RTOR early package(s) need to be submitted to FDA within 6 – 9 weeks. The complete application which includes remaining components not

previously submitted are expected to be submitted within 16 – 20 weeks. The details of RTOR early packages are outlined in [1]. The PDUFA timeline starts once FDA receives the complete application. Typically, feedback and IRs from FDA will be communicated after submission of the RTOR early package. Early interactions through RTOR help the FDA understand the application at an early stage, identify the needs of extra post-hoc analysis, and streamline the review of the final package.

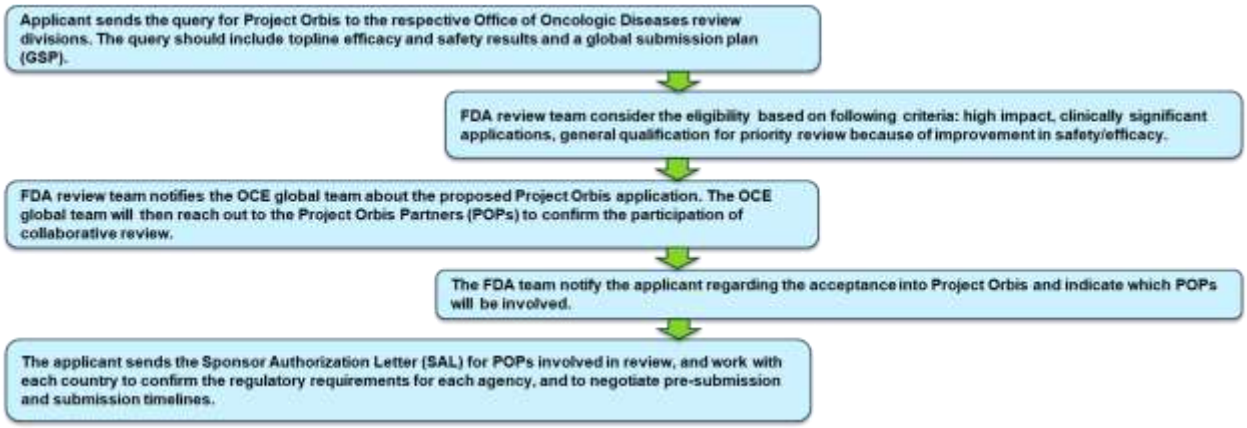
The initial RTOR experience in the drug approvals for 20 oncology applications at FDA Center for Drug Evaluation and Research (CDER) was summarized in [4]. All these applications were qualified for priority review and were approved. Although RTOR acceptance doesn't guarantee early approval ahead of PDUFA schedule, 18 of the mentioned applications were approved early according to PDUFA timelines. Project Orbis was used in 6 out of 20 applications. The positive experience was demonstrated through successful submission of various drug applications. The shortened median approval time for these 20 applications also suggests that the early data access under RTOR contributes to a more smooth and interactive review process.

PROJECT ORBIS

The FDA OCE initiated Project Orbis in May 2019 to provide a framework for concurrent submission and review of oncology products among international partners [2]. Collaborative review among international regulators under Project Orbis makes it possible for patients to get faster access to impactful cancer treatment across the globe. The scope of the Project Orbis includes NDAs, BLAs, and supplemental applications for oncology indications. An application can get nominated for Project Orbis by recommendation from the FDA review team or request by the applicant. The current agencies participating in Project Orbis include Australian Therapeutics Goods Administration (TGA), Brazil's National Health Surveillance Agency (ANVISA), Health Canada (HC), Israel Ministry of Health (IMOH) Pharmaceutical Administration, Singapore Health Sciences Authority (HSA), Switzerland Swissmedic, and United Kingdom Medicines and Healthcare Products Regulatory Agency (UK MHRA). From the Project Orbis Approval information summarized in [5], there are 64 FDA approvals for applications under Project Orbis.

APPLICATION AND PRE-SUBMISSION PROCESS

General steps/processes for Project Orbis application and pre-submission work after nomination are summarized in the following chart. The application should happen after database lock and when TLR is available. This is a required input for Project Orbis query.



SUBMISSION AND REVIEW UNDER PROJECT ORBIS

Once the submissions are done for all Project Orbis Partners (POPs), POPs have regularly scheduled conference calls to collaborate and discuss evaluation of the application. Under the framework of Project Orbis, each HA conducts their own review. Final regulatory decisions, labeling negotiations, and timelines are done independently within each POP. IRs for comment and review are shared between POPs prior to sending out to the sponsor company/local affiliate to avoid duplicates. Once completed, the applicant should share IR response(s) with all involved HAs. The FDA shares review analyses with the other HAs as well, and also tracks the outcome of all Project Orbis applications.

RTOR AND PROJECT ORBIS

RTOR and Project Orbis are two independent programs. Applicants can participate either or both. FDA follows its normal review timelines and processes under Project Orbis, and this won't impact the RTOR timelines. Nevertheless, the use of RTOR with Project Orbis submission can still facilitate early initiation of the FDA review process.

SUBMISSION EXPERIENCE

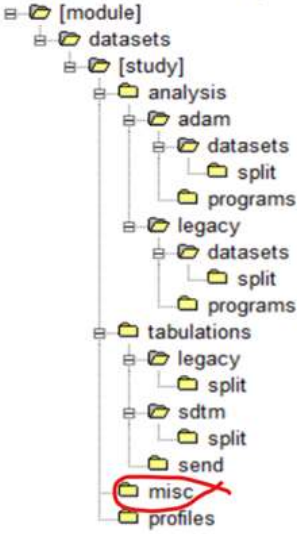
In this section, we will summarize our experience in our 2021-2022 supplement submission with FDA priority review under RTOR and Project Orbis. Our experience aligns with the guidance and information in [1], [2], [3], and [4]. Below is the comparison of our submission experience with the summary statistics in [4], in which the submission and review timelines of 20 oncology applications under RTOR from February 2019 to April 2020 were summarized.

Timeframe		ARASENS submission experience	RTOR experience summarized in [4]		
From	To		Median	Min	Max
RTOR package	Full application	6.3 weeks	5.7 weeks	1.7 weeks	16.2 weeks
Full application	Approval	5.1 months	3.3 months	0.4 months	5.9 months
Clinical data cutoff	RTOR early package	2.8 months	4.2 months	2.1 months	14.6 months
Clinical data cutoff	Full application	4.3 months	6.1 months	2.7 months	15.7 months

Accepted by FDA, there were also some sponsor specific deliverables and activities planned for RTOR submission.

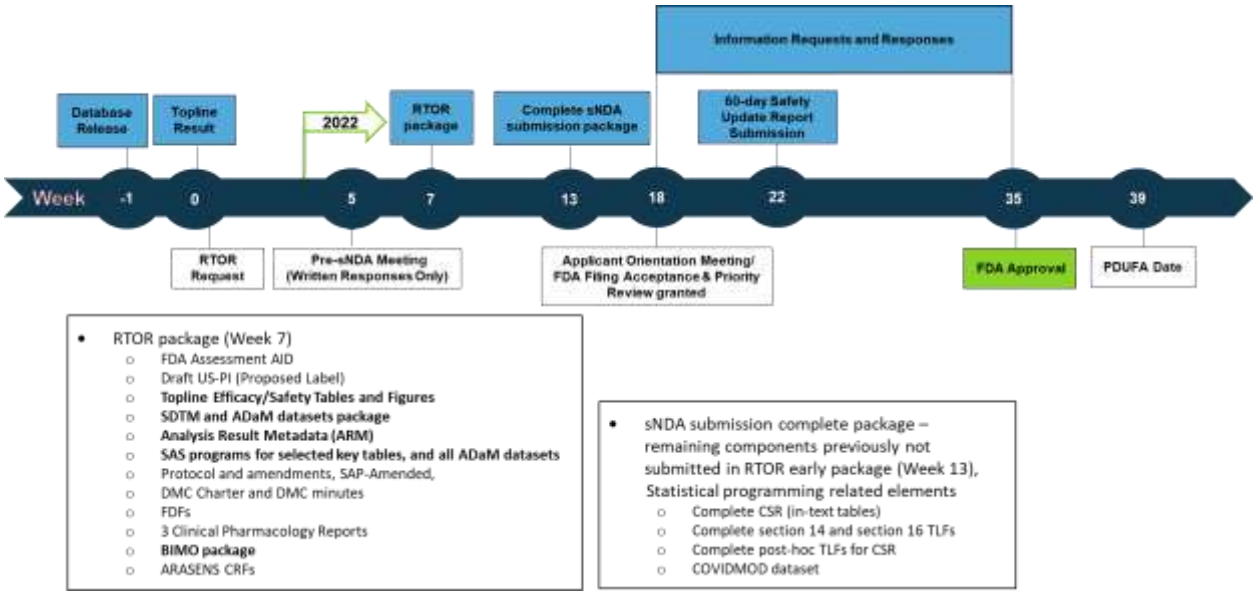
- Bioresearch Monitoring (BIMO) package was included in our RTOR early package. This is an extra element compared to the guideline on [1]. The task owner is generally analytical (e.g., statistical programming) team hence need extra resource planning.
- Early RTOR package was completed in one submission, which was 7 weeks after database release.
- We included the full ADaM package with define.xml, ARM and ADRG in early package. This was beyond the scope of "Complete ADaM datasets for key efficacy and safety tables/figures for pivotal study" suggested in [1]. The decision was based on the consideration of avoiding double work and potential complexities caused by dataset updates between two submission packages.
- Application Orientation Meeting (AOM) was requested by FDA, and was done virtually. The meeting was open for all FDA Oncology staff. In addition, representatives from agencies participating in Project Orbis could attend. Focused discussions on datasets, efficacy and safety analyses happened during the Q&A session. Formal IR with questions from AOM was sent after the meeting from FDA.
- As the clinical trial was conducted during COVID-19 pandemic, there are inevitable COVID-19 pandemic related protocol deviations due to study site-restrictions. Per request from FDA, in addition to the proposed pandemic specific tables, patients who had their data collection affected by the COVID-19 pandemic should be flagged in the datasets. We were asked to provide the COVIDMOD dataset. The purpose of the dataset is to document the date that remote assessments were permitted at the patient and site level. The dataset was submitted in the final sNDA package 5.3.5.1 misc folder. The dataset description/detail and also eCTD location were included in the ADRG Section 4 Analysis Data Creation and Processing Issues under sub-section for "Additional Dataset".

Figure 1: Folder Structure for Study Datasets

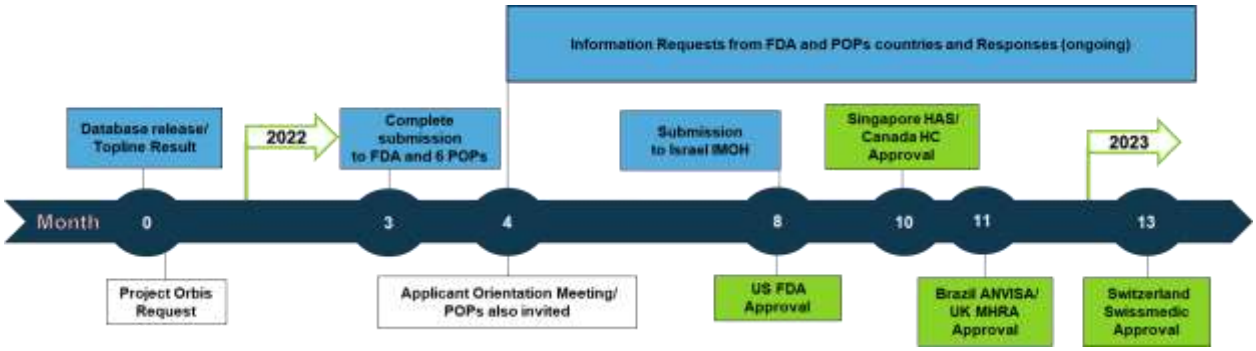


Variable Name	Variable Label	Type	Length	Format Codelist/ Controlled Terms	Source / Computational Method
PatientID	Unique Subject Identifier	C	20.		USUBJIID
Site	Study site identifier	C	10.		SITEID in ADSL domain
ModType	Standardize categories of ModType - derived	C	29.		Modtype='Telemedicine visits' if SVCONTYP = "Phone contact" or "Video contact" in ADSV domain Modtype='Remote labs' if LBEPRELI ='Y' in ADLB domain Modtype='Other - Remote Questionnaires' if QSEPRELI ='Y' in ADQS domain
DateModStart	Start date	N	8.	Date9.	SVSTDT if SVCONTYP = "Phone contact" or "Video contact" in ADSV domain. QSDT if QSEPRELI ='Y' in ADQS domain LBDT if LBEPRELI ='Y' in ADLB domain
DateModStop	End date	N	8.	Date9.	SVENDT if SVCONTYP = "Phone contact" or "Video contact" in ADSV domain QSDT if QSEPRELI ='Y' in ADQS domain LBDT if LBEPRELI ='Y' in ADLB domain

TIMEFRAME ARASENS SUBMISSION UNDER RTOR AND PRIORITY REVIEW



TIMEFRAME FOR ARASENS SUBMISSION UNDER PROJECT ORBIS



LESSONS LEARNED AND RECOMMENDATION

There are many takeaways on our journey of the ARASENS submission under RTOR and Project Orbis programs. The key lessons learned and recommendations are summarized below.

FRONTLOADING PROGRAMMING ACTIVITIES

The turnaround time between FDA confirmation on acceptance of RTOR application and the submission of RTOR early package is very short (9 business days for our case). Once RTOR is initiated and the early package delivered, complete submission package preparation overlaps with incoming IRs from the early package. Frontloading programming activities that start before database release can significantly improve efficiency of submission package preparation. At Bayer, TLR were available for RTOR request within 1 week after database release. All draft programs for datasets, tables, listings, and figures (TLFs) on blinded data were validated and ready for unblinding. Validation on datasets and tables were completed by double programming as needed to improve the efficiency and to assure the quality under accelerated submission model.

ACCELERATED SUBMISSION DOCUMENTS COMPLETION

Cross-functional collaboration and alignment are crucial in the accelerated submission under RTOR and Project Orbis pathway. Early team review of draft tables/figures/listings on blinded data and a stable draft of the clinical study report (CSR) before database release are always beneficial to help achieve cross functional alignment and finalize analyses, which makes it possible to submit full ADaM data package in RTOR early package. In addition, good company standardization significantly increases programming efficiency. The extensive internal macro library supports generating tables, complex figures and submission data documents (e.g., define.xml). All these help the team gain precious time to finalize the CSR shortly after the RTOR early package.

RESOURCE PLANNING FOR EXPEDITED GLOBAL SUBMISSIONS

As much as Project Orbis avoids duplicated queries from participating POPs, it increases the chance of simultaneous IRs from individual POPs due to overlapping review timelines. The team often needs to handle regulatory requests with competing timelines during the reviewing period. Resource needs to be in place ahead of time and balancing between team members for holiday/vacation season. Global team members located in sites across different time zones has a unique advantage to ensure work continuation under aggressive timelines. Regular touch base for cross functional alignment and coordination are also important for operational team to understand context and priority of requests and timeline planning.

Submissions to Japan PMDA and China NMPA were also completed in parallel with the FDA submission (within 1 month) in ARASENS. These countries usually require country-specific analyses, foreign language translation, and/or other local submission requirements (e.g., submission of executable programs). Support and early involvement of the local team is strongly recommended for such a submission plan.

CONCLUSION

The RTOR program initiated by OCE allows early submission of the efficacy and safety topline results and datasets to the agency prior to complete submission. RTOR can also be combined with other review programs including the Assessment Aid and Project Orbis. All these innovative regulatory processes make it possible for the accelerated submission and review, and may contribute to the chance of early access of the approved drugs globally. With RTOR and Project Orbis as part of submission planning, alignment of the cross functional team on the analyses is very necessary to avoid late-stage changes and consequent impact on the statistics and programming. An approved draft CSR would be recommended. Statistical programming activities need to be planned and started early with country specific submission requirements taken into consideration. Resources need to be planned carefully for the busy requests and responses between different HAs with overlapping timelines.

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