

**PharmaSUG 2019 - Paper SS-309**  
**Expediting Drug Approval: Real Time Oncology Review Pilot Program**  
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## **ABSTRACT**

Health care industry aims to provide right treatment and immediate care for a patient. New drug approval in the United States take an average of 12 years from pre-clinical testing to approval with just the approval process averaging around two and half years. It is important to provide patients new, potentially lifesaving therapies at the earliest. To achieve this FDA launched Real Time Oncology Review (RTOR) pilot program which allows FDA to review data earlier, before the applicant formally submits the complete application. For a drug to be selected to be evaluated in the RTOR category it should meet criteria such as easily interpreted endpoints, straight forward study design, drugs showing substantial improvements over available therapy, drugs which have been given break through designation previously. The RTOR process is designed to take about 20weeks of time. Currently, the RTOR pilot program is being used for supplemental applications for already-approved cancer drugs. FDA could later expand the pilot to new drug applications and original biologic license applications for cancer drugs. The RTOR may encourage faster data publication and greater clarity of analysis. Patient, manufacturer and FDA are benefitted by this RTOR scheme. This paper discusses about how RTOR is carried out, challenges faced in a RTOR and why it's being used in the oncology therapeutic area.

## **INTRODUCTION**

As stated by the Prescription Drug User Fee act (PDUFA) VI Reauthorization Letter, the standard review time for drug applications takes around six to ten months. The RTOR was launched in June 2018 by FDA which takes about 20 weeks from the time of RTOR application. RTOR allows FDA to analyze the data even prior to the database lock as soon as the drug makers have topline trial data, thereby reducing the time taken for drug approval. RTOR enables FDA to be ready to approve the new indication upon filing of a formal application with the Agency.

## **RTOR PROCESS REVIEW**

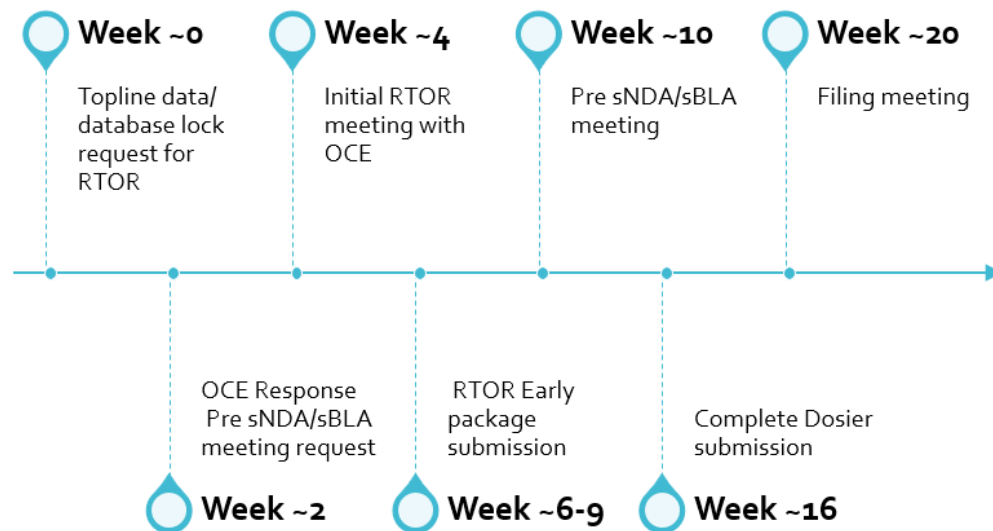
### **ELIGIBILITY CRITERIA**

Considering the timeframe in RTOR scheme, the drugs whose approval is considered for an RTOR pilot program is limited. The decision whether a drug application can be chosen for the RTOR pilot program is jointly taken by clinical division director/deputy director, the review team (including reviewers, team leaders, and management from all relevant review disciplines) and OCE management.

- Drugs 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.
- Straight forward study designs, as determined by the review division and the OCE. Studies conducted exclusively outside the United States and prevention studies will be excluded.
- Endpoints that can be easily interpreted (for example, overall survival in a randomized trial).
- Supplements with CMC formulation changes and supplements with pharmacology/toxicology data will be excluded.
- Submissions with greater complexity, including those with companion diagnostics, may also be excluded for the purposes of the pilot program

## PROCESS

The process adopted for RTOR is faster and efficient. It allows for shorter review and prevents any delay for launch and commercialization. After determination that RTOR is the appropriate review process, the applicant will start sending pre-submission package which includes key raw and derived (ADaM) datasets, including safety and efficacy tables and figures, the study protocol and amendments, and a draft of the prescribing information under the original new drug application (NDA) or biologics license application (BLA), 2-4 weeks after all patient data has been entered and locked in the database. In addition, the applicant should also submit key results, analysis, and datasets for other disciplines (e.g., clinical pharmacology), if applicable. The evaluation of the pre-submitted data is done by FDA for sufficiency and integrity.



## DRUGS WHICH GAINED APPROVAL THROUGH RTOR

Kisqali gained its first approval in March 2017 for HR-positive and HER2 negative advanced or metastatic disease in postmenopausal women. The FDA approved expanded the indication of Kisqali(ribociclib) in combination with an aromatase inhibitor to treat pre/perimenopausal or postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer, as initial endocrine-based therapy on July 18,2018 under RTOR. The FDA also approved Kisqali in combination with fulvestrant for the treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, as initial endocrine based therapy or following disease progression on endocrine therapy. The FDA approved Kisqali in less than one month after the final dossier submission.

Merck's Keytruda got its approval for metastatic non-small cell lung cancer on August 20, 2018 following its full dossier submission on March,23 2018. The RTOR approval is based on KEYNOTE-189, for first-line treatment of metastatic NSCLC with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations in combination with pemetrexed and platinum chemotherapy.

Seattle genetics ADCETRIS® (brentuximab vedotin) in combination with CHP chemotherapy (cyclophosphamide, doxorubicin, prednisone) has made news after its approval from the U.S. Food and Drug Administration (FDA) in less than two weeks. Adcetris previous approval by the FDA is to treat adult patients with previously untreated stage III or IV classical Hodgkin lymphoma (cHL), cHL after relapse,

cHL after stem cell transplant when a patient is at a high risk of relapse or progression, systemic ALCL after failure of other treatment, and primary cutaneous ALCL or CD30-expressing mycosis fungoides after failure of other treatment. Adcetris gained approval under RTOR to treat previously untreated systemic anaplastic large cell lymphoma (ALCL) and other CD30-expressing PTCLs in combination with chemotherapy.

## CHALLENGES

Despite the great strides undertaken in RTOR pilots which have already been implemented, there is a need for expansion of the new settings to achieve best effects of the patients and enhancing improvements in drug development with an aim of improving efficiency. The key challenges involve the adoption of more complex clinical designs which are generally at achieving more complex endpoints and offering simple scenarios entailing companion diagnostics. Companion diagnostics are not being accommodated in the pilot program, which is preventing developers from defining which patients could benefit more from their products.

## ONCOLOGY ARENA

There has been a great need for expediting the development of oncology drug developments to ensure proper and timely patient management process. Further, its utilization in the oncology arena is meant to expedite drug development process and eliminate testing of multiple drugs on multiple subpopulations.

## CONCLUSION

The key challenge facing the FDA in ensuring RTOR runs effectively is the adoption of complex designs which offers a view of new molecular entities in the drug development process. Simple diagnostic scenarios, establishing criteria for increasing complexity will improve scope of RTOR. Processes like aligning CDRH process, manufacturing, inspections and OPDP activities can be considered. Expansion of the RTOR pilot should be done in a stepwise manner by identifying potential barriers and address the problems. The RTOR pilot with no definite timeline might be converted to permanent program by FDA after evaluating success after gaining experience.

## REFERENCES

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