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A Friends of Cancer Research White Paper

REAL-TIME ONCOLOGY REVIEW AND THE ASSESSMENT AID:

INCREASING REVIEW EFFICIENCY THROUGH STANDARDIZATION AND EARLIER DATA ACCESS

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INTRODUCTION*

The regulatory review process for pharmaceutical drugs is a resource intensive undertaking for both the drug sponsor and the United States Food and Drug Administration (FDA) that assesses the drug's benefit and risk. Improvements in the efficiency of the process can have significant impact on the resources and time required to complete a drug review, consequently, bringing new therapies or new therapy indications to patients more quickly. There are currently several tools that the FDA can employ to expedite certain applications, including fast track designation, breakthrough therapy designation (BTD), accelerated approval, and priority review designation, Table 1. The FDA Oncology Center of Excellence (OCE) has established two new pilot projects with voluntary participation to test novel approaches to regulatory review for oncology drugs, the Real-Time Oncology Review (RTOR) and the Assessment Aid (AAid).

The RTOR Pilot Program aims to improve the efficiency of the review process for supplemental applications through data and analysis standardization and early iterative engagement between the FDA and applicant by allowing for the submission of key efficacy and safety tables/figures and datasets prior to the complete dossier submission. Eligible applications include oncology supplements for drugs or biologics likely to demonstrate substantial improvements over available therapies (e.g. BTD, accelerated approval, and priority review designation-eligible indications) and based on clinical trials with straightforward study designs and easily interpretable endpoints

* The considerations for possible future expansion of the Real-Time Oncology Review and Assessment Aid pilots presented in this whitepaper should not be construed as final FDA policy.

ABOUT FRIENDS OF CANCER RESEARCH

Friends of Cancer Research drives collaboration among partners from every healthcare sector to power advances in science, policy, and regulation that speed life-saving treatments to patients.

(for example, overall survival in a randomized trial), as defined by the Review Division. The pilot will include applications to be reviewed by Division of Oncology Products 1, Division of Oncology Products 2, and Division of Hematology Products. The first two RTOR approvals were supplemental approvals for KISQALI® (ribociclib)[1] for two new indications, based upon two randomized, placebo-controlled, phase III trials with progression free survival endpoints, and KEYTRUDA® (pembrolizumab)[2] based upon a randomized phase III trial compared to chemotherapy with progression free survival and overall survival endpoints. Both applications showed unequivocal efficacy results. Both KISQALI® (Kisqali) and KEYTRUDA® (Keytruda) had previously received BTD and priority review designation, whereas Keytruda had also previously been granted accelerated approval for other indications.

The second OCE pilot is the AAid for new drug applications (NDA) and biologic license applications (BLA) submissions or supplements (sNDA/sBLA). The AAid can improve review quality and efficiency by providing a shared document into which the applicant can insert their positions and the FDA review team can subsequently layer in their assessment, which reflects their critical evaluation. Participation in the AAid pilot can occur in conjunction with the RTOR pilot or independently.

Both pilot programs may ultimately be converted to permanent programs (there is no definitive timeline for the pilot); however, the full value of the pilots will be realized from expansion beyond their initial, limited scope. The FDA will need to accumulate more experience with the pilots to fully assess their success, but should consider priorities of the various drug development stakeholders, Table 2, when determining metrics for success to inform expansion. It will be important to consider how the review phase is defined in the RTOR context and implications to statutory obligations. Metrics for success should not be limited; however, to the review phase but should reflect benefits of RTOR as it may extend to other phases of the drug development pathway, including clinical development and the post-marketing phase. Although the pilots are still in their early stages and have not defined specific timelines, the ultimate benefit of this novel approach to regulatory review will likely be demonstrated through earlier patient access to important therapies if it is expanded to NDAs/BLAs.

Table 1: Regulatory Review Mechanisms

	Accelerated Approval	Fast-track Designation	Priority Review	Breakthrough Therapy Designation	Summary Level Review
Eligibility	1. Treat serious or life-threatening diseases 2. Provide meaningful therapeutic benefit over existing therapies 3. Surrogate endpoint reasonably likely to predict clinical benefit	1. Intent to treat broad range of serious diseases 2. Potential to fill an unmet medical need	1. Offer major advances in treatment over existing therapies	1. Treat serious or life-threatening diseases 2. Early clinical evidence of substantial improvement over existing therapies	Supplemental applications that: 1. The FDA determines the existing data is acceptable to demonstrate safety, and 2. The data used to develop the qualified data summary is submitted to the FDA 3. Not eligible for use with RTOR
Designation	No formal process	Can be requested by sponsor at any time; FDA has 60 days to respond	Requested by sponsor at time of NDA/BLA submission; FDA has 45 days to respond	Can be requested by sponsor at any time after IND submission; FDA has 60 days to respond	Supplemental applications for a qualified indication for a drug that the FDA determines to be appropriate for summary level review
Clinical Development	Conditional approval granted using surrogate endpoints from phase II trials or interim phase III data; controlled trials with hard clinical endpoints required to confirm clinical benefit	Earlier and more frequent communication	Not applicable	Abbreviated or condensed development; earlier and more frequent communication; delegation of senior reviewers and cross-disciplinary review team	Not applicable
Review Process	NDA/BLA data submitted in one package; standard 10-month review	Option for rolling NDA/BLA submission; official review clock begins when last module is submitted	NDA/BLA data submitted in one package; review time shortened to 6 months	NDA/BLA data submitted as they are accumulated; review time shortened	The FDA may rely upon qualified data summaries submitted as part of a sNDA/sBLA to support the approval of a supplemental application, with respect to a qualified indication

Table 2: Potential Impact of Real-time Oncology Review on Drug Development Programs

Stakeholder	Review Phase	Clinical and Post-Approval Programs
Regulatory Authority	• Pinpoint areas for focused review • Improved review quality	• Earlier access to trial data and supportive documents • Identify opportunities and concerns sooner
Sponsor/ Applicant	• Interactive/iterative process • Earlier feedback from FDA before dossier submission on data and review focus	• Increased predictability • Ability to address concerns sooner • Opportunity to further develop clinical program, data submission, etc. with collaborative feedback from the FDA
Patients	• Increased confidence in safety and efficacy data	• Earlier access to therapies

CASE STUDY: **NOVARTIS**

The first approval made through the RTOR pilot was ribociclib (trade name: Kisqali). On July 18, 2018, the FDA expanded the indication for ribociclib combination with an aromatase inhibitor for pre/perimenopausal women with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative advanced or metastatic breast cancer, as initial endocrine-based therapy. FDA also approved ribociclib in combination with fulvestrant for the treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer as initial endocrine therapy or following disease progression on endocrine therapy. Ribociclib was previously approved for postmenoposal women with HR-positive, HER2-negative advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine therapy and received BTD. The ribociclib sNDA was submitted to expand the indication based upon results of two phase III studies, one to support each indication change. Under the RTOR pilot, many components of the submission dossier were submitted as pre-submission materials, on a periodic basis (Table 3). The early submission from Novartis not only included efficacy and safety data, but also a clinical pharmacology package including pharmacokinetic and drug-drug interaction data. Once these components were received, the FDA review team analyzed the data for quality and integrity and verified the sponsor's results and conclusions. In addition, the FDA also conducted their own analyses. Novartis and FDA scheduled regular, bi-weekly teleconference meetings, eliminating the need for typical applicant orientation and mid-cycle meetings. The FDA approved the sNDA in less than one month following final dossier submission. The Novartis sNDA was also the first to use the AAid, discussed later in this whitepaper.

Table 3: Novartis RTOR Timeline

Event Date	Action	Notes
January 2018	Pre-NDA meeting held with FDA	
April 6, 2018	Novartis/FDA RTOR discussion	
April 24, 2018	Pre-submission packages start to be sent to FDA	• Safety and Efficacy datasets • Draft labeling • Module 2 summary documents and safety reports • Module 4 components • Clinical pharmacology package • Clinical study reports • 90-day safety update datasets
April-June 2018	FDA issues multiple IRs	
June 28, 2018	Full dossier submission	• Financial disclosures and BIMO information • Annotated USPI
July 18, 2018	sNDA for Kisqali approved	

CASE STUDY: **MERCK**

Pembrolizumab (Trade name: Keytruda) has been granted 13 BTDs including two for pembrolizumab monotherapy for non-small cell lung cancer (NSCLC). Merck was granted accelerated approval under a priority review timeline in May 2017 for pembrolizumab for first-line treatment of patients with metastatic NSCLC in combination with pemetrexed and carboplatin. Accelerated approval was based upon the KEYNOTE-021 trial cohort G and KEYNOTE-189 was identified as the confirmatory trial. Full approval was granted for pembrolizumab, 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 through the RTOR pilot. The approval was granted approximately 1 month prior to the Prescription Drug User Fee Act (PDUFA) assigned action date for a priority review designation. Merck and the FDA determined the components of a pre-submission package as part of a meeting to discuss the RTOR pilot (Table 4). The pilot was a collaborative process that included more frequent contact between the FDA project manager and Merck regulatory contact.

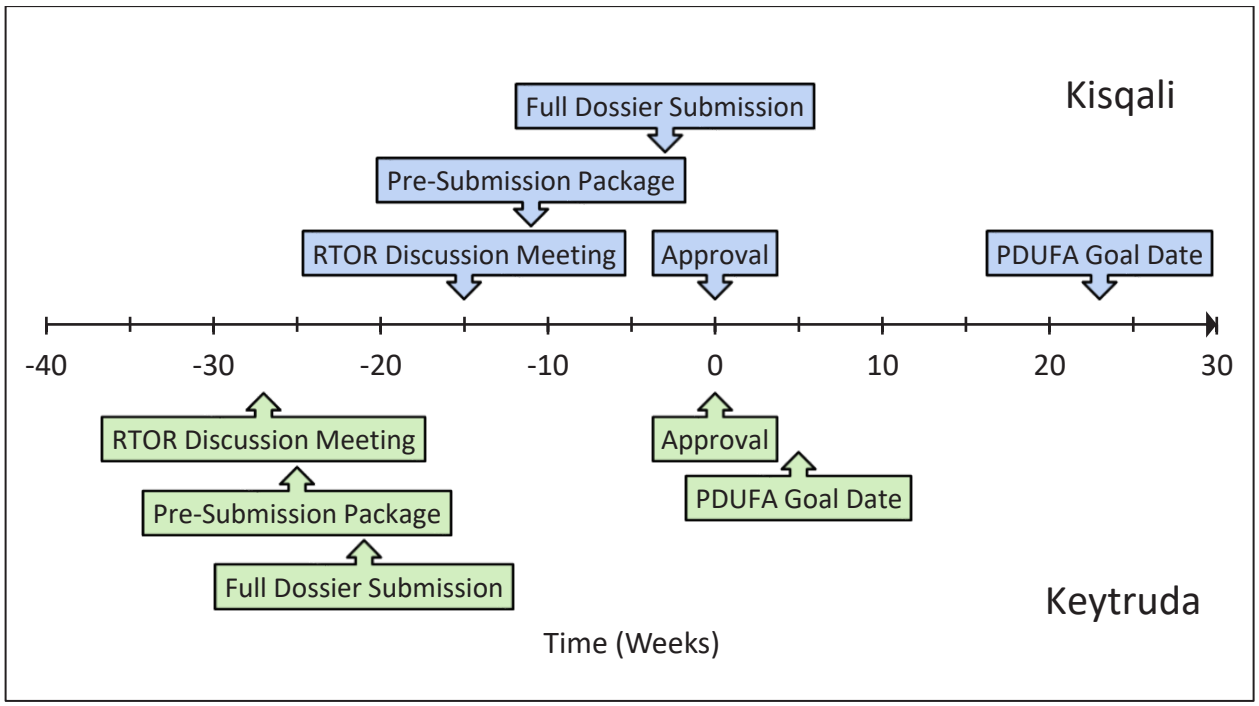
Table 4: Merck RTOR Timeline

Event Date	Action	Notes
January 2018	Informed FDA of topline results from KEYNOTE-189	Indicated intent of sBLA submission based on KEYNOTE-189
February 2018	Merck/FDA RTOR discussion	Determined data components and contents of the pre-submission package
February 27, 2018	Pre-submission package sent to FDA	• Key efficacy and safety tables and figures • SDTM dataset package and supporting documentation • Draft USPI • ADaM datasets and SAS programs • Protocol including all amendments and the SAP • DMC meeting minutes • Case report forms
February - March 2018	FDA issued IR regarding USPI and request for PMC	
March 23, 2018	Full dossier submission	• Included annotated USPI • OSI and Financial Disclosure information • Module 2 documents and CSRs
August 20, 2018	sBLA approved	

LESSONS LEARNED

The early examples that have informed this RTOR pilot have allowed for data and document submissions prior to final dossier submission, providing the FDA with additional time to begin evaluating results as they were submitted (Figure 1). Access to the SDTM and ADaM datasets, and draft USPI were important components of the pre-submission package. The agency was then able to submit IRs to the sponsor to fill in the gaps as the data was reviewed, allowing for ongoing communication between the agency and sponsor and quick response/submission of information and additional analyses by the sponsor as requested by the FDA. The IRs that were issued to both sponsors primarily related to the USPI and study datasets. Both Merck and Novartis indicated that submitting general comments/information related to data derivation, such as grouped terms provided in the draft USPI, earlier in the pre-submission communication along with additional documentation accompanying datasets may have helped to facilitate FDA review. Additionally, earlier submission of the data definition files would be desirable, where possible.

Figure 1: Timeline for RTOR submissions*



* Similar timelines are not guaranteed for all RTOR pilot submissions

PILOT EXPANSION

Expansion of the RTOR pilot should be approached in a stepwise fashion as the FDA and industry gain more experience with a "front-loaded" application process. Initially, the FDA could consider expanding eligibility from supplemental applications with straightforward clinical trial designs and easily interpretable endpoints to more complex supplemental applications such as those that include more complex clinical trial designs, more challenging endpoints, or a companion diagnostic claim. With more experience troubleshooting complex supplemental applications, the FDA could consider expanding eligibility to simple Breakthrough-designated New Molecular Entity (NME) NDAs/BLAs and, eventually, increasingly complex NDAs/BLAs (Table 5). If the RTOR pilot is ultimately expanded to NME applications, impact to other aspects of the drug development pipeline, including clinical trial design, will need to be addressed.[3-4] Eventually, as we gain more scientific knowledge and achieve more data standardization, other evidence such as patient-experience data (e.g., collected through patient-reported outcomes) and other real-world data, could be integrated to the RTOR to foster a comprehensive benefit-risk assessment of a product.

A key to efficient expansion of the RTOR pilot project will be to capitalize on the successes and lessons learned from pilot submissions to identify potential barriers to expansion and recommend policy to address those barriers.

Table 5. Mock Plan for RTOR Expansion

RTOR	Pilot 1 Scope	Pilot 2 Scope	Pilot 3, etc. Scope	Final Pilot Scope
Pilot Timeframe	2018	2019		
Criteria for Inclusion	• sNDA/sBLA for drugs likely to demonstrate substantial improvements over available therapy (e.g., BTD, priority review designation, or accelerated approval-eligible designations) with: ○ Straight forward study designs, as determined by the review division and the OCE, and ○ Endpoints that can be easily interpreted (for example, overall survival in a randomized trial)	• Drugs likely to demonstrate substantial improvements over available therapy (e.g., BTD, priority review designation, or accelerated approval-eligible designations) with: ○ Complex study designs or simple diagnostic scenarios based upon a prospective trial that demonstrates efficacy of a drug in a biomarker defined population using an approved CDx test measuring the same marker and tissue type (e.g., Pfizer's dacomitinib approved with Qiagen therascreen EGFR test for NSCLC), or ○ Simple diagnostic scenarios based upon an approved therapy in a new indication (line extension) via a prospective trial that demonstrates efficacy in a biomarker defined population using a new diagnostic test	• Establish criteria for increasing complexity	• NMEs with BTD • Complex study designs • Single arm study designs • RWE and PROs
Exclusions	• Diagnostics • RWE • CMC supplements • NME	• CMC supplements • RWE • NMEs	• NMEs	
Considerations		• Align CDRH processes	• Align manufacturing processes	• Align manufacturing processes and inspections • Align clinical site inspection processes • Align OPDP activities to ensure earlier submission and review of first 120-day marketing materials if single arm studies will lead to accelerated approval

Aligning Manufacturing Processes with Real-Time Oncology Review

In an expedited approval setting such as BTD, it is important to align and synchronize product development with commercialization in order to successfully realize needed acceleration. Aligning product development and commercialization can be challenging in the setting of an expedited approval pathway such as RTOR when data is requested earlier than during a traditional development and review program. Lessons from the implementation of BTD could inform policies for expedient alignment and implementation (Box 1).

Box 1. Recommendations for Manufacturing Processes for Expedited Pathway [Dye et al. AAPS PharmSciTech (2016) 17(3)]

1. Encourage more flexible approaches to ensuring information exchange and understanding to facilitate expediting development and review
2. Agree upon schedule of important review milestones and turnaround timeframes for information requests
3. Discuss approach to submit agreed upon data packages during the review:
   a. Submission of the dissolution method development report and dissolution specification setting strategy for early review by FDA Biopharmaceutics reviewers
   b. Additional real-time stability data on commercial product
   c. Additional batch data to support validation
4. Initiate discussions to enable more rapid access to CMC and facility data to facilitate pre-approval inspection scheduling and conduct

Additionally, it is important to note that, dependent upon the potential pilot candidate (i.e., NDA or BLA), the request for certain information may vary. These potential differences would be discussed in meetings with the FDA prior to submission of the pilot candidate. Table 6 outlines manufacturing components and readiness to consider during the different phases of a drug development program.

There are two key issues for early communication of manufacturing data: 1. early agreement upon an appropriate timeline for submission of manufacturing data, which will necessitate prioritization of product stability and batch data and facility inspections; and 2. identification of components that can be addressed in post-approval commitments.

Table 6. Manufacturing Components and Readiness

Phase	Component
Pre-submission	• Analytical method development and validation* • Commercial to-be-marketed formulation • Container/closure system for commercially marketed product • Product specification • Stability and degradation studies • Representative batch data • Manufacturing process development, description of intended initial processes and controls • Facility information for assessment
Submission	• Submit comparability strategy/protocol for post-approval site changes • At least one executed batch record • Demonstration of successful manufacturing using processes and controls representative of intended initial commercial operations • Updated primary stability data • Rolling submission of process validation information
Post-Approval	• Process and formulation optimization • Concurrent release of process performance qualification lots[5]

* Control strategy, acceptance criteria, and methods may still be evolving at this stage.

To accommodate the accelerated submission timeline described, sponsors will need to prospectively design CMC development such that process and product improvement and optimization require minimal comparability assessment while keeping the following aspects in mind:

- **Optimize candidate selection**
  - Physical-chemical properties and pharmacokinetic profile of small molecule drugs
  - Screening and engineering out hot spots for degradation or undesired modifications for biologic drugs

- **Leverage platform knowledge** - Ensure fit of candidate molecules into manufacturer's platform for drug substance and drug product and related processes to improve speed and robustness

- Consider additional in-process and specification tests in the control strategy to balance uncertainty driven by accelerated product/process development. It is envisioned that additional controls could be removed post approval when adequate product/process knowledge has been accumulated and its evaluation indicates a stable and capable process and control strategy

- **Leverage use of Physiologically Based Pharmacokinetic (PBPK) models to enable rapid development of drug products with optimal performance** – The models can be applied to support formulation optimization and other changes required during fast moving development programs (e.g. PSD, manufacturing process, scale-up, etc.)

- **Initiate key activities early:**
  - Activities needed to address non-platform behavior and/or unusual product and process characteristics
  - Assessment of CQAs
  - Identification of launch sites for drug substance and drug product or consider launch from R&D facilities while ensuring product quality and patient safety with reliable supply and pre-approval inspection readiness

- **Focus on reliable supply of quality product at launch**

Aligning Inspections Processes with RTOR for Pilot Expansion to NMEs

An additional area of focus in the aim of removing barriers in getting products to patients are the BIMO Good Clinical Practice (GCP) and manufacturing site pre-approval inspections that currently occur on the critical path to approval (manufacturing pre-approval inspection readiness was addressed in the previous section). GCP pre-approval inspections involve retrospective evaluation by the FDA of the sponsor study monitoring practices and procedures post-submission (typically 3-5 months to organize and execute) to determine compliance with applicable regulations.

Proactive information sharing with the FDA (earlier submission of site level datasets, inclusion of sponsor GCP quality assurance briefing as part of submission, and sharing of quality assurance data output in real time during pivotal study conduct) to enable faster assessment of GCP compliance, could save on resources for both the sponsor and the FDA, while further expediting timelines.

Aligning CDRH Processes with RTOR for Pilot Expansion to NMEs

A great deal of work has already been undertaken to align CDRH processes for BTD. CDRH review mechanisms such as modular Premarket Approvals (PMAs), which enable review and acceptance of submission components in advance of the clinical validation data, are successful for aligning review of companion diagnostics with drug approvals and will continue to be valuable for RTORs. However, development and market-ready distribution of a diagnostic at the time of approval may not be feasible. Given the increasing number of targeted therapies in development in oncology, it bears considering how drug/diagnostic co-development, review, and approval can be coordinated within the RTOR pilots and eventually be established as practice.

- Use of previously approved tests will enable swift review of new therapeutic indications. To this end, pharmaceutical companies can reach out to key diagnostic companies and clinical laboratories to bring tests in as follow-on companion diagnostics. This will increase the number of readily available diagnostic partners for development of new CDx indications.[7]

- Post-market commitments may extend the opportunity to bring a validated test to market. Points to consider for planning post-market device validation would include:

    - Adequately banking specimens from patients eligible for the trial to enable swift validation of the final *in vitro* diagnostic (IVD).

    - In the case of very rare biomarkers (e.g. ROS1), increasing availability of well-annotated specimen biobanks will enable improved access to tissues with rare biomarkers needed for analytical validation studies to support the diagnostic. Where specimen banking is not feasible, use of clinical specimens from an equivalent patient population may be feasible.

    - Move toward study designs that stratify patients based on the biomarker using an analytically validated test. Development of study designs that can be implemented would focus on

complementary device claims rather than companion diagnostic claims. Complementary device claims can then be supported in the post-market setting with specimens from subjects in the trial. This would enable line extension based on retrospective analysis and/or RWE that shows increased efficacy for patients with a certain biomarker or genomic profile (e.g., micro satellite instability (MSI) or tumor mutational burden (TMB)). Study designs should remain consistent with CDER review; issues include the target population, sample size, endpoints, and statistical analyses for missing samples.

- Ideally, understanding the value of the biomarker to patient management with the therapeutic by pre-planning clinical trials that stratify patients on the biomarker would also enable FDA to evaluate the magnitude of relative treatment benefit through an interaction effect between the biomarker and drug efficacy. Such a study design would allow identification of a clinically meaningful threshold, which could allow faster contemporaneous co-approval of companion tests with the therapeutic that support the efficacy. Such an approach may be able to pave the way for obtaining additional robust analytical validation in the post-market setting because the clinical utility and cut-off of the test for the biomarker is well supported.

Data Standardization

Facilitation of a more efficient submission and review pathway for expansion of the RTOR pilot should be accompanied by better data standardization and a more iterative submission process for improved communications between the sponsor and agency. For example, an iterative process for updating drafts of the USPI may be necessary in the pre-submission setting. Using CDISC data format for key datasets, such as adverse events, demographics, treatment response, exposure, etc., while allowing legacy data format for other datasets may facilitate a smoother transition during data standardization. In the future, data standardization that would be beneficial to realizing the full potential of the RTOR might include universal protocols, electronic case report forms, and data formats in an effort to streamline processes for better clinical trial design, data submission, and review. Development and adoption of dynamic interactive analysis tools will be essential to facilitating data standardization for efficient communications. Such tools could aid the agency's review of the data and analyses more efficiently with an option to extract the programming codes for understanding of the data derivation and statistical methodology applied in the analyses. Encouraging companies to include the interactive analysis tools, such as R-Shiny in the RTOR pilot will ultimately lead to the development of industry-wide interactive analysis application.

Adequate preparation will be necessary on the part of both the FDA and sponsor to efficiently expand

RTOR. For the FDA to review greater volumes of pre-submission data, earlier engagement with the Office of Pharmaceutical Quality will be necessary and the agency will need to facilitate earlier international inspections of clinical trial sites and manufacturing facilities. Also, the FDA will need to address how to expand beyond supplemental applications where agency reviewers are already familiar with efficacy data, safety signal identification, clinical trial design, and data structure and format for approved drugs.

Similarly, drug/biologic sponsors will need to identify process improvements necessary to enable earlier dataset preparation for pre-submission data sharing and the type of data, particularly manufacturing data, that would be feasible to share during pre-submission. Finally, sponsors will need to consider the implications of pre-submission data-sharing on clinical trial design and whether adjustments will need to be made in trial design to enable earlier formatting of clinical data.

ASSESSMENT AID

In addition to the RTOR pilot program, the Novartis sNDA submission for Kisqali was also the first approval using AAid pilot** (Table 7).

Table 7. Novartis Assessment Aid Timeline

Date	Action	RTOR Action
Early April, 2018		Pre-submission package sent to FDA
April 24, 2018	Novartis received Assessment Aid template	
June 5, 2018	Novartis completed Assessment Aid	
June 28, 2018	FDA returned agency feedback on Assessment Aid to Novartis*	Full dossier submission
July 6, 2018	Novartis submitted Assessment Aid to FDA with final updates*	
July 18, 2018		sNDA for Kisqali approved

* This is a special case because both the agency and applicant were exploring the best practice for use of the AAid. Once submitted, the applicant would generally not have the opportunity to revise their portion of the AAid.

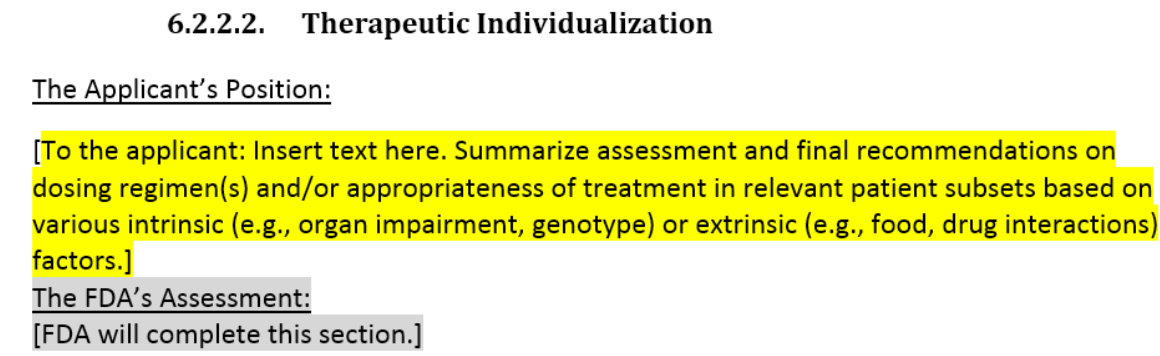
The AAid is a form, developed based on the FDA Multidisciplinary Review template, which covers the critical regulatory components that need to be evaluated to make approval decisions and labeling recommendations. Most sections of the template are divided into two parts, clearly delineated to emphasize the ownership of each position:

1. The Applicant's Position
2. The FDA's Assessment

** The Merck sBLA was part of the RTOR pilot but not the AAid. The AAid was not developed at the time that Merck entered the pilot for RTOR and the regulatory review was well under way when the AAid pilot became available.

The separation of the applicant's positions and FDA's assessment is intended to clarify (1) the ownership of each statement and (2) agreement/disagreement between the applicant and the FDA's position (Figure 2). The AAid template is sent to the applicant during the Investigational New Drug (IND) phase (for example, around the pre-NDA/BLA meeting). The applicant then adds their position to the template in preparation for the NDA/BLA or sNDA/sBLA submission. When the AAid is used in conjunction with the RTOR pilot, the applicant can submit the document before the formal sNDA/sBLA submission. Otherwise, the document is submitted at the time of the NDA/BLA or sNDA/sBLA submission or shortly thereafter. The FDA review team, after conducting their scientific analysis, then inputs their assessment into the same document, expounding upon areas of disagreement and additional findings in the FDA's analyses. The AAid can help focus the FDA review on critical assessment, rather than repeating the applicant's data analyses for improved review efficiency and consistency.

Figure 2: Section 6.2.2.2: Therapuetic Individualization



6.2.2.2. Therapeutic Individualization

The Applicant's Position:

[To the applicant: Insert text here. Summarize assessment and final recommendations on dosing regimen(s) and/or appropriateness of treatment in relevant patient subsets based on various intrinsic (e.g., organ impairment, genotype) or extrinsic (e.g., food, drug interactions) factors.]

The FDA's Assessment:

[FDA will complete this section.]

Figure 2: Section 6.2.2.2 in the Assessment Aid Template. Sections of the AAid are divided into two parts (The Applicant's Position and The FDA's Assessment) and are clearly delineated to emphasize the ownership of each position. Instructions to the applicant are provided in some sections to clarify the FDA's expectations of what should be included.

While successful at increasing review efficiency in this initial case study, the maximum benefit from inclusion in future submissions will be from expanded uses. For example, a potential application of the AAid could be to consolidate documents submitted by FDA and the sponsor to the Oncology Drug Advisory Committee (ODAC) to provide more streamlined briefing document materials for ODAC members and the public. Further, the AAid could be expanded to incorporate additional analyses of patient reported outcomes to inform benefit-risk assessments of NDAs/BLAs. Future considerations for the AAid will be how IRs and updates to the company position will be addressed and how the completed AAid will be communicated to the sponsor after regulatory action has been taken.

CONCLUSION: PATHWAY FORWARD FOR PILOT EXPANSION

Great strides have been made in regulatory policy with the implementation of expedited programs, such as accelerated approval, breakthrough therapy designation, priority review, and fast track designation, to streamline the development and review of new therapies, but further optimization can still be achieved. Results from the first two RTOR supplemental application approvals and first use of the Assessment Aid garner optimism regarding the utility of both pilots to furthering this goal. However, the greatest value from both pilots will be gained from expansion into new settings where patients can achieve the greatest benefit from improvements in drug development and clinical trial designs for sustained efficiency. By expanding the complexity of the RTOR pilot in a robust and step wise approach, both FDA and the sponsor can gain valuable understanding and practice to ensure increased efficiency gains can be maintained, while also ensuring the quality of the review and risk-benefit decision. Ultimately, successes from the expansion of these programs can be an example for optimization by other health authorities and global harmonization to enable a greater number of patients to benefit from earlier access to important new drugs likely to demonstrate improvements over existing therapies.

TABLE GLOSSARY

ADaM – analysis data model
ASAP - Administrative Systems Automation Project
BIMO – bioresearch monitoring
CDRH – Center for Devices and Radiological Health
CDx – companion diagnostic
CMC – chemistry, manufacturing, and control
CQA – critical quality attribute
CSR – clinical study report
DMC – data monitoring committee
IR- information request
OSI – Office of Scientific Investigation
PAS – prior approval supplement
PDUFA – Prescription Drug User Fee Act
PMC – post-marketing commitment
SAP – statistical analysis plan
SAS – statistical analysis software
sBLA – supplemental BLA
SDTM – study data tabulation model
sNDA – supplemental NDA
USPI – US Prescribing Information

REFERENCES

[1] KISQALI® is a registered trademark of Novartis Pharmaceuticals Corporation (Novartis)

[2] KEYTRUDA® is a registered trademark of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. (Merck)

[3] US Food and Drug Administration. (2018). *Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics Guidance for Industry - DRAFT GUIDANCE*. Retrieved from https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621817.pdf?elqTrackId=1B8C5F95655CFB4E33D74C16AA376B41&elq=2f5ae25cb11a4c4594af5320a932d7af&elqaid=5289&elqat=1&elqCampaignId=4225

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