Paper SA02

Lessons learned from FDA Real Time Oncology Review Pilot Program: A Novartis & Roche perspective

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ABSTRACT

In 2018, FDA Oncology Center of Excellence launched Real Time Oncology Review (RTOR) pilot program. RTOR aims to improve the efficiency of the review process for supplemental applications by allowing for the submission of key efficacy and safety tables/figures and datasets prior to the complete dossier submission. Novartis and Roche have gone through FDA RTOR in recent times: Novartis Kisqali supplemental New Drug Application was approved less than one month after submission and one of Roche's RTOR submissions, CLL14, was approved 10 weeks after full submission. This presentation will aim to share learnings from the unique cross-company experiences from both submissions: We will explain what RTOR is; how different the two submissions were; describe the challenges faced; and finally provide recommendations to others.

INTRODUCTION

FDA Oncology Center of Excellence initiated Real Time Oncology Review pilot (RTOR), early 2018. This paper explains what RTOR pilot is. It discusses the RTOR pilot's impact on programming aspects by sharing experiences from two supplemental New Drug Applications (sNDA): Novartis Kisqali® and Roche CLL14. The focus of the paper will not be on describing the studies but rather on the planning and programming strategies taken to deliver the filings as part of RTOR.

WHAT IS REAL-TIME ONCOLOGY REVIEW (RTOR)?

Real-Time Oncology Review is a pilot program launched by FDA OCE. As specified in FDA's website, it "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." [1]
This process consists in an early engagement between FDA and applicant by submitting key efficacy and safety tables/figures and datasets prior to full application submission.

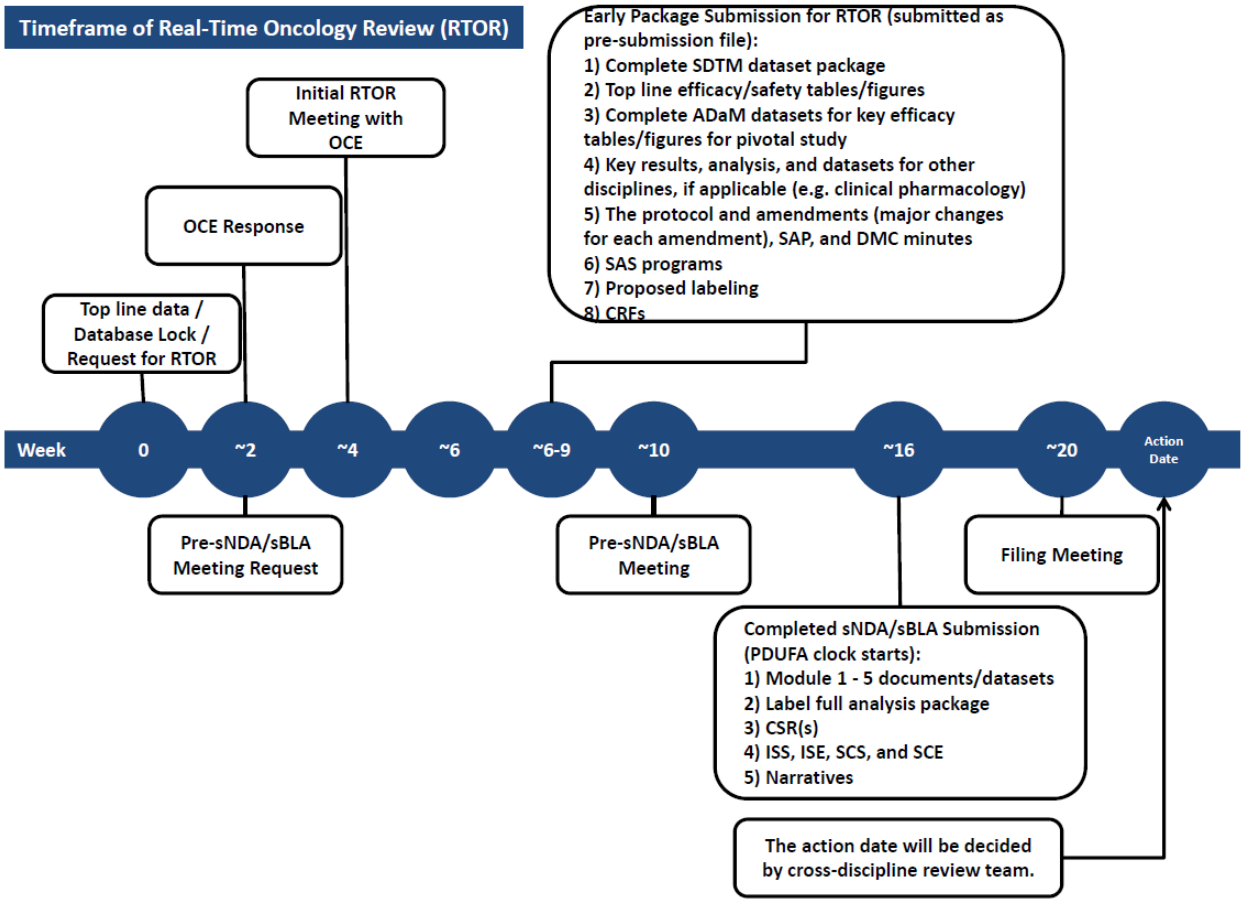
ELIGIBILITY CRITERIA

As of September 2019, original and supplemental New Drug Applications and Biologic License Application may be selected for the RTOR assuming the following criteria are met:

- Drugs likely to demonstrate substantial improvements over available therapy
- Straight forward study designs
- Endpoints that can be easily interpreted

Studies conducted exclusively outside the US as well as neoadjuvant and prevention studies are excluded. Finally, supplements with chemistry, manufacturing, and control (CMC) formulation changes are not eligible for RTOR.

RTOR'S PILOT TIMEFRAME



Source: FDA[1]

KISQALI EXPERIENCE

BACKGROUND

Kisqali supplemental New Drug Application (sNDA) was driven by two pivotal phase III studies:

- CLEE011E2301 (MONALEESA-7): Phase III randomized double-blind, placebo-controlled study of ribociclib in combination with tamoxifen / non-steroidal aromatase inhibitor (NSAI) and goserelin for the treatment of premenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer who received no prior endocrine therapy for advanced disease.
- CLEE011F2301 (MONALEESA-3): Phase III randomized double-blind, placebo-controlled study of ribociclib in combination with fulvestrant for the treatment of men and postmenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer who have received no or only one line of prior endocrine therapy.

By January 2018, both MONALEESA-7 and MONALEESA-3 trials met their primary endpoint of progression-free survival (PFS). Top Line results were shared with FDA.
Combined submission for expansion of two new indications was planned for June 2018.

RTOR: HOW IT STARTED?

Early April 2018, FDA introduced Real Time Oncology Review pilot program to Novartis. Indeed, Kisqali sNDA has been identified as potential candidate by FDA. At that time, this initiative was new, no approval happened through RTOR yet. Novartis accepted to take part of it and started working on pre-submission deliverables planning. FDA also scheduled bi-weekly teleconference meetings with Novartis.

RTOR: PROGRAMMING ASPECTS

This section describes the impact of RTOR on statistical programming team supporting MONALEESA-7 and MONALEESA-3. It does not cover clinical pharmacology package as it was handled by a different programming team within Novartis.

From data standard perspective, both MONALEESA-7 and MONALEESA-3 studies were CDISC-compliant. In addition, they followed similar structure as CLEE011A2301, MONALEESA-2 trial, which supported original NDA, approved the year before (March 2017).

When RTOR discussion started with FDA, SDTM and key ADaM (Analysis Data Model) datasets of MONALEESA-7 and MONALEESA-3 studies were finalized. Nevertheless, creation of CRT package was ongoing. It was not possible to send define.xml for the two pivotal studies in timely manner. Define components (e.g. reviewer's guide) were not finalized. Define.xml creation itself being outsourced, it gave us less flexibility in completion timelines. After consultation with FDA, they agreed to receive datasets without expected documentation. So, we decided to follow an ad hoc approach:

- SDTM documentation: Most datasets being standard and custom domains being aligned with original NDA submission pivotal study, MONALEESA-2, no SDTM specification would be sent.
- ADaM documentation: Specification of key ADaM variables would be explained in an excel file.

At the end of April 2018, all SDTMs, key efficacy and safety ADaM data sets were submitted to the agency. As agreed, pre-submission package did not include define.xml.

From then onwards, FDA issues information requests. Some questions were related to derivation done in analyses. Those may have been avoided if pre-submission package included define.xml. Indeed, some queries were addressed in reviewer's guide and/or Analysis Results Metadata (part of ADaM define.xml).

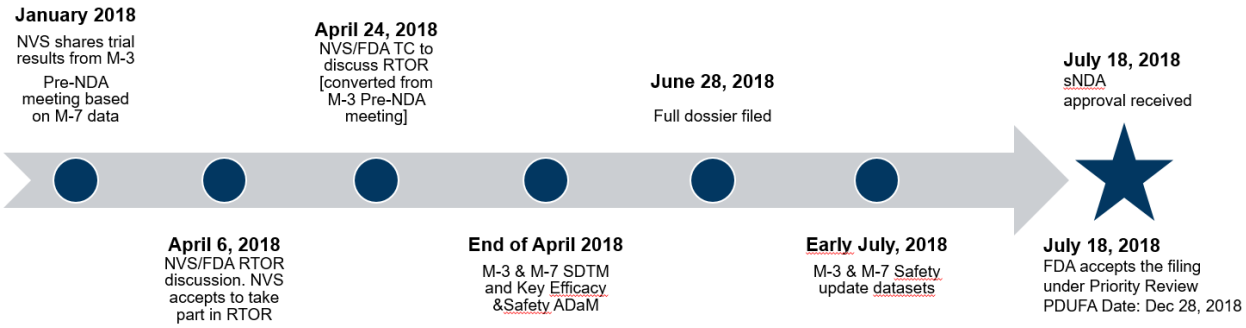
OUTCOME

Full dossier has been submitted on June 28, 2018. Kisqali received approval for expanded indication on July 18, 2018[2]. It was the first cancer drug approved through RTOR program.
KISQALI is a kinase inhibitor indicated in combination with:

- an aromatase inhibitor for the treatment of 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; or
- 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.

KISQALI KEY TIMELINES

Kisqali did not follow proposed RTOR timelines as team has been introduced to this pilot program few weeks after MONALEESA-3 results have been shared with FDA.



CLL14 EXPERIENCE

BACKGROUND

Venetoclax sNDA was driven by the pivotal CLL14 phase III study:

A multicenter, open-label, randomized Phase 3 trial, which was conducted in close collaboration with the German CLL Study Group (DCLLSG), evaluated the efficacy and safety of a combined regimen of venetoclax and obinutuzumab (n=216) versus obinutuzumab and chlorambucil (n=216) in previously-untreated patients with CLL and coexisting medical conditions. The therapies were administered for a fixed duration of 12 months for venetoclax in combination with six cycles of obinutuzumab. The trial enrolled 445 patients, all of whom were previously-untreated according to the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria. The primary endpoint was progression-free survival (PFS) based on investigator assessment, using iwCLL criteria.

HOW IT STARTED

CLL14, like various other filings had a variety of deliverables that the team had to work on e.g. programming analysis datasets and respective outputs as part of the CSR; providing supportive study data/analysis as part of the filing; setting up some safety pooling between the studies; continuously working with internal and external stakeholders and so on.

The team was busy with programming activities, when approximately. 5-6 months prior to Database Lock (DBL) we heard about the RTOR pilot announcement from the FDA. As a result, the question was asked to our team: is it feasible for our potential filing to be submitted as part of RTOR pilot?

NON-CDISC VS. CDISC?

Saying ‘Yes’ was very difficult to answer. Firstly, this had never been done before in the entire company and very new across the industry too, so it was difficult to refer to any real use-cases. Secondly and perhaps our biggest challenge, the terminology used by the RTOR guidance was CDISC i.e. SDTM and ADaM. Our data was pre-CDISC mandate and as a result was expected and agreed to submit the dataset package in a non-CDISC format, based on SDTM-like and ADaM-like data. So then the question turned into: what would it take to turn our data into a CDISC submission?

This was an equally challenging question; how much effort it would take to convert all our programming, for source and analysis data to comply with CDISC standards? After much research the answer was: converting to a CDISC submission would take us beyond the planned filing date. The data was not designed to be CDISC conformant to begin with and the challenge would have been too large to retrospectively change everything into SDTM and ADaM within the current timelines.

Our proposal was to proceed with our non-CDISC filing as originally planned. Our Regulatory team (and other Biometrics functions) were concerned that this could be a risk and we should go for CDISC. So we were getting to a point where we just could not agree on the approach.

HYBRID CDISC APPROACH

Our eSubmission (eSub) Lead had suggested another approach that could work. It has been successfully submitted on another filing and accepted by the FDA following a pre-agreement with the FDA on the data format. The proposal was to convert our SDTM-like datasets into CDISC SDTMs compliant format, as the source data, since it would be the very first thing FDA would review. With regards to our ADaM-like data, we would create an CDISC ADaM compliant ADSL dataset and all other analysis datasets would remain as ADaM-like. Together with the datasets we provided the associated Define.xml file, which addressed any technical rejection criteria concerns. Together with this file we also provided the SDTM annotated CRF (aCRF) and both the Study Data Reviewers Guide (cSDRG) and the Analysis Data Reviewers Guide (ADRG). Note: as per pre-submission file requirements, for our analysis data, we had planned to submit only subject level characteristics and efficacy, as well as provide software programs used to create the primary and secondary endpoints (for both datasets and tables and figures). Everything else would follow in the full filing package.

We called this approach internally 'CDISC-Acceptable' as a way of defining this hybrid CDISC submission. Finally, we would also need to ensure our datasets complied to CDISC standards by running the validation conformance checks on all the SDTM datasets and the ADaM ADSL dataset. We did this using Pinnacle 21 Enterprise®. This approach would also work within our DBL timelines, so as per RTOR timeframe recommendations, we had agreed to be ready by Week 6 (after top line results announced) if RTOR was accepted by FDA.

So then the question was: should we (Biometrics) create all this additional work for ourselves when we do not even know if FDA will accept us for RTOR? It was a tough decision to make as there was a lot of work involved in a short amount of time. Ultimately, we decided that we should take this on as a smart-risk, as if we do get acceptance to RTOR, then the benefit of FDA seeing our data earlier could lead to faster approval and patients getting treatment quicker. We also acknowledged that if the FDA rejected RTOR then we would still carry on towards our filing timelines and it just meant we would be in a much better position to be eSub ready for the full filing package. By taking this approach it also helped us gauge the time and effort that would be required if we had to do this on another molecule.

RTOR: REJECTION

Following all programming activities, learning new tools, countless meetings and many late nights we approached DBL and following the release of our topline results, the great news was that our trial met its primary endpoint. This was fantastic news for patients, for the company and also for the team who put in a tremendous amount of effort to get to that stage. After that, we knew that we would be submitting a request for RTOR to the FDA as soon as we could. The programming team was still in the midst of preparing the filing package for the FDA, when approximately 2 weeks after our request for RTOR, the FDA review team responded back and rejected RTOR for us.

The rationale was around questions they had on Safety, which meant that this might not be a straight-forward review (as part of the eligibility criteria for RTOR). The wider CLL14 team had felt they had covered this following initial submission of results to FDA, but also responded back following the questions/concerns.

This was a disappointing outcome, hard felt by Biometrics, due to the effort put in by everyone. As mentioned previously we knew this could happen and the plan was always to continue with the CDISC-acceptable approach as we still felt this would facilitate an easier review for FDA, so we did not do any less once we heard the decision.

RTOR: RECONSIDERED

Approximately a couple of months later, we received feedback from the FDA following our responses. They stated they were happy with our responses to their questions and offered us RTOR. This was quite a surprise as we were not expecting it and it also put us in a unique position to potentially submit all our data, earlier than our intended filing timelines and that was asked to us. Referring back to the original RTOR deliverables, we were required to submit the topline results/data, however, since we had prepared for this early enough, we were in a position to submit all data, including supportive study and pooled datasets.

OUTCOME

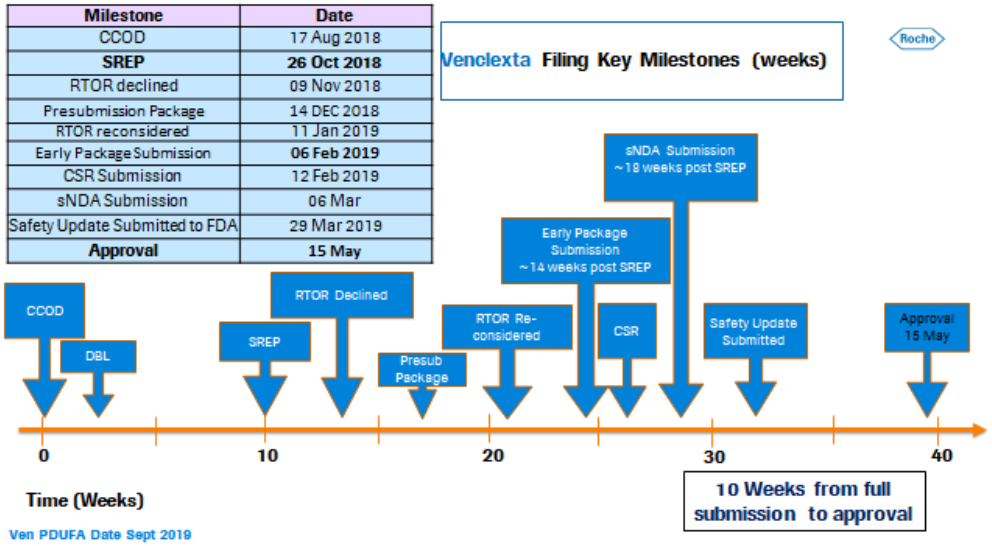
On May 15, 2019, the Food and Drug Administration approved venetoclax[3] (VENCLEXTA, AbbVie Inc. and Genentech Inc.) for adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

Approval was based on CLL14, a randomized (1:1), multicenter, open label, actively controlled trial of venetoclax in combination with obinutuzumab (VEN+G) versus obinutuzumab in combination with chlorambucil (GClb) in 432 patients with previously untreated CLL with coexisting medical conditions.

FDA used the Real-Time Oncology Review and Assessment Aid Pilot Program for this application and granted priority review as well as orphan drug and breakthrough therapy designations. Approval was granted 3.7 months ahead of the PDUFA (Prescription Drug User Fee Act) date.

CLL14 KEY TIMELINES

Milestone	Date
CCOD	17 Aug 2018
SREP	**26 Oct 2018**
RTOR declined	09 Nov 2018
Presubmission Package	14 DEC 2018
RTOR reconsidered	11 Jan 2019
Early Package Submission	**06 Feb 2019**
CSR Submission	12 Feb 2019
sNDA Submission	06 Mar
Safety Update Submitted to FDA	29 Mar 2019
Approval	**15 May**



Note: SREP = Study Results Endorsement Plan, which means the same as topline data being released/unblinded.
CCOD = Clinical cut-off date

RTOR: CHALLENGES

KISQALI SPECIFICITIES

- Lack of RTOR knowledge: Team participated to RTOR in early stage of the pilot. As such, there were lots of questions raised: What can be submitted? How early can it be submitted? What are the risks to send data without adequate documentation? Those were discussed during internal cross-functional meetings. In addition, regular teleconferences with FDA helped us to adjust pre-submission deliverables.

- Answer information requests while finalizing define.xml: Programming team would usually work on CRT package for filling and support health authority questions afterwards. In our case, key programmers were involved in multiple high priority activities at the same time: information requests, finalization of CRT packages as well as preparation of safety updates. This resulted in long hours to have everything completed in time.

CLL14 SPECIFICITIES

- As described earlier, one of the biggest challenges was taking the risk to plan upfront for RTOR in mind for CLL14.

- Learning CDISC deliverables: Our eSub process and deliverables were done in-house but the CLL14 programming team had limited experience in CDISC submissions, so we had to learn more about the Analysis Data Model (ADaM; to create ADSL) and gain a better understanding of the validation conformance checks that need to be performed on the dataset to comply with CDISC standard. As we had invested in purchasing licenses for Pinnacle 21 Enterprise®, we had to learn more about that tool and its capabilities as well as eSub deliverables that get created from it e.g. Analysis Data Reviewers Guide (ADRG).

COMMON CHALLENGES

- Working on multiple priorities: a challenge faced by many but both Kisqali and Venetoclax teams were stretched on the submission study deliverables as well as other studies on the molecule. When plans were made regarding resourcing they were made without considering RTOR. However, having unexpected requests on other studies which had to be delivered or onboarding new team members were difficult challenges we had to deal with during programming work.

- Late changes to analyses: CLL14 did not have numerous instances of changes to analyses but some were significant that it had an impact on re-programming as well as additional pressure in still sticking to original timelines. It was difficult having to manage CSR programming, conformance checking, pooling work and then having to go back and make changes to programming derivations that were agreed previously. From Kisqali perspective, late changes in CSR or pooled analyses delayed finalization of CRT packages.

RTOR: OPPORTUNITIES

KISQALI OPPORTUNITIES

- Early confirmation of right approach: MONALEESA-2 study was used as a reference for sNDA even though some of the data standards have changed in the meantime. This approach may have helped early review of FDA as they were familiar with original NDA data.

CLL14 OPPORTUNITIES

- Lack of substantial FDA Information Requests (IRs): the only request the programming team received was for additional program code for certain endpoints; which were provided as readable code. The low number of questions was surprising for us and there could be various reasons for this but one reason we felt might be due to the structure and content of the eSub package we delivered:
    - Structure: Having submitted as ‘CDISC-acceptable’, we submitted in a structure the FDA are familiar with
    - Content: Originally the plan was to submit only a few datasets but since FDA reconsidered RTOR later down the line, we were able to submit everything, so it meant less risk of them asking us for additional data

COMMON OPPORTUNITIES

- One of the first RTOR pilots: Being part of a pilot that could support earlier availability of medications to patients is very motivating. All of the learnings from RTOR were shared with other teams who could face similar challenges in the future.

- Educating stakeholders about what we do: sometimes the perception of stakeholders outside of Biometrics is that programmers click a button and everything magically appears! With RTOR and all the deliverables we had to produce, it was a great opportunity to bring awareness to all the work being done behind production of tables, figures and listings: datasets creation, documentation, processes and tools, as well as challenges faced with late changes to analyses

RECOMMENDATIONS

Following experiences from Kisqali and CLL14, we would like to provide the following recommendations to others who may go through RTOR or any filings:

- Plan with eSub in mind: Be aware of CDISC eSub dataset package content and format requirements from the onset and embed the creation and maintenance of the files into the study lifecycle. Programming efforts can be typically focused on getting the analysis datasets and the subsequent outputs ready for the CSR. However, the mindset needs to change and to consider eSub readiness and adherence to CDISC from the very beginning e.g. run conformance checks as soon as data is available. With RTOR, there are no new deliverables that need to be produced as part of the eSub; it is more about sharing key data earlier. In order to meet such timelines, it is important to be eSub ready by DBL.

- Explain to stakeholders what is involved in statistical programming: this should happen really early, in the planning stage of programming activities. Doing so they can understand what happens in our work and ensure they plan accordingly for their work; understanding the potential knock-on impacts down the line for programming. Biometrics are heavily involved in the RTOR deliverables, hence, it is important to explain this so that we can work effectively together.

- Freezing planned analyses 1 month before DBL: the idea behind this is to reduce the risk of late changes and/or additions post DBL. It is key to ensure there is further onus on all stakeholders to do a thorough review of planned analyses ahead of time. Of course, there may be cases where changes are required but then it is important to communicate the knock-on impact of making late changes. Indeed, we may need to be ready 6 weeks after DBL to send the RTOR eSub package to the FDA. We should focus on filing efforts rather than re-programming analysis.

- Plan resources ahead of time: resourcing is never an easy task but adding extra resources to a team during 'fire-fighting' is never ideal. It puts pressure on the existing programming team/leads to onboard the new members during busy times as well as the new team members to perform very quickly. One may consider having extended team members: programmers already trained to project specificities who could support based on workload requirement.

- Consider de-prioritization of other deliverables: if there are several priorities and teams are trying to deliver on all fronts, there can be a risk of quality; burnout of team members; or not even meeting any deliverables. It is worth considering what could be 'dropped' if the full focus should be on the filing. Not an easy thing to raise or accomplish but always worth discussing with stakeholders beforehand if conflicting priorities arise.

REFERENCES

[1] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program
[2] https://www.fda.gov/drugs/resources-information-approved-drugs/fda-expands-ribociclib-indication-hr-positive-her2-negative-advanced-or-metastatic-breast-cancer
[3] https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-venetoclax-cll-and-sll

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