Perspectives in Regulatory Science and Policy

Title: Project Orbis: Global Collaborative Review Program

Authors: R. Angelo de Claro[1,2], Dianne Spillman[1], Lauren Tesh Hotaki[1], Michael Shum[3], Laila Sofia Mouawad[4], Gustavo Mendes Lima Santos[4], Kelly Robinson[5], Melissa Hunt[5], Caroline Healy[5], Agnes Chan[6], Yee Hoo Looi[6], Clare Rodrigues[6], Ulrich-Peter Rohr[7], Chantal Walther[7], Richard Pazdur[1,2]

Running Title: Year One Experience

Author Affiliations: [1]Oncology Center of Excellence and [2]Office of Oncologic Diseases, U.S. Food and Drug Administration, [3]Therapeutic Goods Administration (Australia), [4]Brazilian Health Regulatory Authority (ANVISA), [5]Health Canada, [6]Health Sciences Authority (Singapore), [7]Swiss Agency for Therapeutic Products (Swissmedic)

Corresponding Author: R. Angelo de Claro, MD, U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993. Phone 301-796-4415. Fax: 301-796-9909. E-mail: Romeo.Declaro@fda.hhs.gov

Conflict of Interest/Disclosure Statement: There are no conflicts of interest or disclosures for all authors.

Word Count: 233 (abstract), 2687 (body)

Number of Tables and Figures: 4 (2 tables and 2 figures)

Abstract:

In 2019, the FDA Oncology Center of Excellence (OCE) launched Project Orbis, a global collaborative review program to facilitate faster patient access to innovative cancer therapies across multiple countries. Project Orbis aims for concurrent submission, review, and regulatory action for high-impact clinically significant marketing applications among the participating partner countries. Current Project Orbis partners (POP) include the regulatory health authorities (RHA) of Australia, Brazil, Canada, Singapore, and Switzerland. Project Orbis leverages the existing scientific and regulatory partnerships between the various regulatory health authorities under mutual confidentiality agreements. While FDA serves as the primary coordinator for application selection and review, each country remains fully independent on their final regulatory decision. In the first year of Project Orbis (June 2019 to June 2020), a total of 60 oncology marketing applications were received, representing 16 unique projects, and resulting in 38 approvals. New molecular entities, also known as new active substances, comprised 28% of the received marketing applications. The median time gap between FDA and Orbis submission dates was 0.6 months with a range of -0.8 to 9.0 months. Across the program, the median time-to-approval was similar between FDA (4.2 months, range 0.9 to 6.9, N=18) and the POP (4.4 months, range 1.7 to 6.8, N=20). Participating countries have signified a strong commitment for continuation and growth of the program. Project Orbis expansion considerations include the addition of more countries and management of more complex applications.

Introduction

The U.S. Food and Drug Administration (FDA) Oncology Center of Excellence developed Project Orbis to collaborate with international regulatory health authorities (RHA) to facilitate the submission, review, and approval of oncology products in other countries. The program aims to deliver faster patient access to innovative cancer treatments across the globe.

RHA partners at the program start in May 2019 were the Therapeutic Goods Administration (TGA) and Health Canada (HC), the RHA of Australia and Canada, respectively. In December 2019, Project Orbis expanded to include the RHA from Singapore and Switzerland, which are Health Sciences Authority (HSA) and Swissmedic (SMC), respectively. In May 2020, Brazil's RHA, Brazilian Health Regulatory Agency (ANVISA) joined Project Orbis.

Prior to Project Orbis, the RHA of Australia, Canada, Singapore, and Switzerland (ACSS) had formed the ACSS Consortium in 2007. The ACSS Generics and New Active Substance (NAS) Working Groups established a work-sharing initiative to handle the increasing workload and complexity of marketing applications (1). FDA leveraged the existing collaboration within ACSS for the selection of the initial countries to participate under Project Orbis.

Project Orbis builds on the existing international regulatory collaboration for oncology drug development between FDA and counterpart RHA (date of establishment of FDA oncology collaboration) from the European Union (2004), Canada (2010), Japan (2014), Australia (2014), and Switzerland (2016). Prior to Project Orbis, the FDA international collaboration primarily

consisted of monthly 90-minute teleconferences to briefly discuss several marketing applications, also known as dossiers, submissions, or drug applications, that are under review in each country. With Project Orbis, the interactions have been expanded to include direct collaboration with the application review, including the use of a core review document to facilitate discussion. Each RHA remains fully independent with regard to the regulatory decision-making for each application under their jurisdiction.

This article describes the implementation of Project Orbis and discusses the challenges and future directions for the program. This article also summarizes the initial experience (June 2019 to June 2020) with Project Orbis, which was used to support the submission of 60 oncology marketing applications (original drugs and new indications) and 38 approvals across the Project Orbis countries (USA, Australia, Brazil, Canada, Singapore, Switzerland).

Project Orbis Implementation

Because Project Orbis involves discussions on confidential aspects of marketing applications, each participating RHA is required to have a confidentiality agreement with all other RHA in the Project Orbis working group. All written and verbal communications as part of Project Orbis are subject to the confidentiality agreements and cannot be disclosed without written permission of the FDA or the information owner.

Selection of applications for Project Orbis is coordinated by FDA, and initial queries received by RHA are referred to the FDA. Either the FDA or the US Sponsor, the primary contact for FDA,

can propose an application for Project Orbis once topline results are available from the registrational clinical trial(s). FDA also requests the Sponsor to include the global submission timing and plan that includes the name and contact information for each of the Sponsors or Sponsor-affiliates responsible for the country-specific submissions. FDA then sends the proposal (topline results and global submission plan) to the RHA to confirm interest and availability for participation. Sponsors also have the discretion to select the number of RHA (minimum of 2, must include the FDA) for submission. After confirmation with the RHA, FDA will confirm the global submission plan through the US Sponsor and designate the participating RHA formally as a Project Orbis Partners (POP) for that application. The Project Orbis Working Group (POWG) for each application will consist of FDA and the participating POP.

Participation of FDA and at least one other RHA is required for a marketing application to be considered as a Project Orbis application. The program initially accepted supplemental applications, also known as variations or indication extensions, that add new indications to previously approved drugs. In December 2019, new molecular entities, also known as new active substances, were accepted into the program.

Clinical criteria for FDA selection of applications for Project Orbis include high-impact and clinically significant applications. Project Orbis applications are generally expected to meet the criteria for FDA priority review. Qualifying criteria for FDA priority review include: the drug is intended to treat a serious condition and if approved, would provide a significant improvement in safety or effectiveness (2).

Project Orbis requires a common platform to facilitate the review of the same marketing application across the participating countries. The marketing application should be submitted electronically to each RHA using the Common Technical Document format (e.g., eCTD) with all documents in English, with possible exception for country-specific Module 1 (3). Each marketing application should also conform to the respective domestic submission requirements. An additional requirement (for Type A or B Orbis submissions) is use of the Assessment Aid (AAid) document, which would serve as the core document for POWG discussion and as the primary review document for FDA (4).

There are several types of Project Orbis submissions that have evolved and are dependent on the timelines between FDA and the POP (Table 1). During the initial implementation of the program, marketing applications were submitted concurrently or near-concurrently (within 30 days) to FDA and the POP. These applications are termed as Type A Orbis (Regular Orbis) and requires submission of the marketing applications to the participating countries within 30 days of the FDA submission. Type A Orbis allows for maximal collaboration during the review phase. Marketing applications submitted through Project Orbis but associated with expected delays of > 30 days on the application submission and/or regulatory action > 3 months of the FDA action date are termed as Type B Orbis (Modified Orbis). Finally, for applications where FDA already took regulatory action, there is Type C Orbis (Written Report Only Orbis) which allows FDA to share their completed review documents with the POP.

For Type A and certain Type B Orbis applications, FDA schedules and coordinates several multi-country teleconferences to discuss various aspects of the application. These include a kickoff meeting and application-specific meetings. The kickoff meeting, which is scheduled before or within 30 days of FDA application submission, discusses the overall review strategy and review timelines within the POWG. FDA provides for the verification of the clinical trial results by analyzing the submitted tabulation and analysis datasets. The next milestone meeting is the midcycle meeting where FDA review disciplines present the key findings from the analyses, followed by discussion with the POP. Additional Orbis meetings include discipline-specific meetings (e.g., efficacy, safety, clinical pharmacology) and overall benefit-risk, where relevant sections of the AAid are discussed. For Type B Orbis submissions, the number of multi-country meetings depends on the entry timeline of the POP with the ongoing FDA review. For Type C submissions, the above meetings do not occur because FDA regulatory action has already been completed for the marketing application.

Each POP remains fully independent with regulatory decision-making to adhere to country-specific laws, regulations, ordinances, and/or policies. As a result, these may result in differences in the approval or rejection of marketing authorization, the wording of the indications, and approval of other labeling content across the POP. While the AAid is able to accommodate assessment differences by delineating assessments from each POP, the use of the AAid as an evaluation report remains under the discretion and regulations by the POP. Negotiations of labeling and postmarketing requirements are also independently handled by each POP.

Project Orbis: First Year Experience

The results below represent the Project Orbis workload based on the first-year set of 21 oncology marketing applications received by FDA from June 12, 2019 to June 12, 2020. Regulatory actions from the POWG (FDA + POP) and the corresponding 39 marketing applications received by the POP through August 15, 2020 are included in the analyses.

Project Orbis received a total of 60 marketing application submissions in its first year of implementation (Figure 1), categorized into 16 unique projects. Five of the 16 unique projects included up to 2 application submissions which may have included the cross-labeling application for products administered in combination, and for FDA purposes, submissions that sought multiple indications. The median number of POP was 2 with a range of 1 to 4 per marketing application. TGA and HC were the most common POP with receipt of 14 and 12 applications, respectively. The majority of application submissions (72%, N=28) to the POP were Type A.

Through August 15, 2020, there have been a total of 38 approvals across Project Orbis (Figure 1). Of the 20 Orbis approvals, 19 were Type A submissions and one was a Type C submission. The remainder of the applications (N=21) remain under review (pending status).

All of the applications selected by FDA for Project Orbis met criteria for FDA priority review. Additional FDA Expedited Programs such as Breakthrough Therapy Designation and the Real-

Time Oncology Review program were utilized in 62% and 71% of the FDA applications, respectively (2, 5, 6). The 21 FDA applications received under Project Orbis represent approximately one-third of the priority review oncology workload at FDA during the same time period.

Project Orbis received 17 new molecular entity (NME), also known as new active substance (NAS) submissions, corresponding to 6 unique NME/NAS products in the first year of the program. Project Orbis NME/NAS workload comprised 28% of the total workload. For NME/NAS applications, Project Orbis also implemented the use of a CMC (Chemistry, Manufacturing, and Controls) version of the AAid in addition to the multi-disciplinary AAid.

Major oncology disease categories were represented in the Orbis submissions, including solid tumor and hematologic malignancy indications. The most common oncology indications in Project Orbis (number of application submissions) were non-small cell lung cancer (N=10), chronic lymphocytic leukemia (N=10), acute myeloid leukemia (N=6), endometrial cancer (N=6), breast cancer (N=5), and hepatocellular cancer (N=5).

Comparison of the submission and approval dates for FDA and the POP showed minimal lag times (Figure 2) between the FDA and the POP for Type A applications. For the 39 Orbis applications submitted to the POP, the median time gap between FDA and POP submission dates was 0.6 months with a range of -0.8 to 9.0 months. The breakdown according to Orbis Type is shown in Figure 2, with a median submission time gap of 0.4, 2.7, and 5.5 months for

Type A, B, and C submissions, respectively. For Type A applications, 90% of the POP applications were submitted within 1.1 months of the FDA submission date.

The median time gap for approvals for Type A applications between FDA and the POP was 1.1 months, with 90% of the approvals conducted within 2.4 months of the FDA approval date. Time-to-approval analyses showed similar metrics between FDA and the POP overall and separated by type of application (NME/NAS versus supplement/variation) (Table 2).

Discussion

Through close collaboration between the RHA, Project Orbis demonstrates that the delay in marketing application submission and approval in Orbis countries can significantly be reduced, with several applications achieving parity or near-parity with FDA timelines. Analyses of NME/NAS marketing applications from 2015-2019 noted a median overall gap time (submission and approval) of 6.4, 8.4, and 9.5 months for HC, TGA, and SMC compared to FDA (7). For Type A applications under Project Orbis, the median overall gap time (submission and approval) was 1.5 months, with a 90th percentile of 2.8 months between FDA and the POP. This increased efficiency was achieved using the available resources within each RHA.

Collaboration within Project Orbis is optimized with concurrent submission and review of the marketing applications. This is supported by the finding that 95% of the approvals by the POP were Type A Orbis where concurrent application submission is required with plans for concurrent review and, where feasible, action with the FDA. However, this requires additional

pre-submission coordination between the Sponsors and the RHA. Ideally, marketing applications for Project Orbis should be identified at the time of availability of the topline efficacy and safety results from the pivotal or registrational clinical trial(s). A common reason for non-participation of an interested RHA for an Orbis application review is that the Sponsor does not have adequate resources to submit the application to that RHA.

Additional workload considerations for Sponsors include the coordination of responses to information requests which may originate from multiple RHA. This is partially mitigated by sharing of information requests and through the collaboration that occurs during the Project Orbis meetings. For example, FDA has conducted additional analyses based on the request of the POP.

For Project Orbis applications, the FDA review conduct is unchanged compared to non-Orbis applications, with FDA reviewing all sections of the AAid and verifying the results based on analyses of the study reports and datasets. The additional workload to FDA with use of Project Orbis occurs with the addition of the multi-country meetings before and during the review cycle. FDA time-to-approval metrics (Table 2) for Orbis applications are consistent with FDA metrics for non-Orbis applications, with multiple applications receiving approval months ahead of PDUFA (Prescription Drug and User Fee Agreement) deadlines. Through Project Orbis, FDA has obtained independent perspectives from POP on regulatory and clinical considerations for oncology marketing applications. In addition, approval of clinically significant oncology

therapies could facilitate the design and conduct of clinical trials that are more relevant to the US population, particularly with availability of more current therapies for control arms.

A limitation of Project Orbis would be the resources involved with review and meeting coordination within the POWG. For some applications, RHA have declined to participate due to workload prioritization brought about by the recent COVID-19 pandemic. Nevertheless, the overall resource utilization for a POP could be less under Project Orbis as compared to a stand-alone review. While FDA cannot delegate any of the review responsibilities for a marketing application review, the regulatory framework of the POP allows for leveraging of assessments of effectiveness and safety by a major regulatory agency such as the FDA or the European Medicines Agency (EMA) in their regulatory decision making.

Participation in Project Orbis requires reasonable alignment of review processes and use of the AAid as a core document for discussion. FDA has not reached out to EMA to participate in Project Orbis due to differences in review processes between the FDA and EMA. It would be challenging to accommodate the EMA review clock stops under the continuous review timeline for Project Orbis. Another potential reason for non-participation of some RHA would be the Project Orbis requirement for the marketing application and review documents to be in English.

Future Directions

Based on the first-year experience with Project Orbis, all of the current participating countries have expressed strong interest with continuation and growth of the program. With increased

application workload and participation of multiple RHA, it is important to periodically assess the progress and metrics of the program. Representatives from each of the participating RHA meet quarterly to review the overall program status and also discuss potential modifications to the current process.

Possible areas for expansion for Project Orbis involve participation of other countries, and handling of more complex applications, such as those that involve companion diagnostic devices or advanced therapy products such as cellular and gene therapies. It would be important to be aware of an inflection point where a critical mass of participating countries or applications is reached that reduces the review efficiency achieved with Project Orbis. Likewise, the regulatory framework for in vitro diagnostic devices and advanced therapies would add to the complexity of Project Orbis review.

Project Orbis demonstrates that global regulatory collaboration is attainable and can deliver faster access to new therapies for patients with cancer across multiple countries. Reduction of the regulatory approval gap through Project Orbis represents an initial major step for expediting patient access. A possible future direction for Project Orbis would be earlier interactions with health technology assessment bodies that determine coverage decisions.

Extension of the collaborative efforts to other aspects of oncology drug development, including clinical trial endpoints, trial designs, enrollment criteria, and postmarketing surveillance can also be considered. Finally, the core principles learned from Project Orbis are applicable to

281 other global health concerns such as the COVID-19 pandemic where global regulatory

282 collaboration would be of high public health relevance.

References:

1. ACSS (Australia-Canada-Singapore-Switzerland) Consortium. Bern (Switzerland): Swissmedic. Available from https://www.swissmedic.ch/swissmedic/en/home/about-us/international-collaboration/multilateral-co-operation-with-international-organisations---ini/multilateral-co-operation-with-international-organisations---ini.html [cited September 15, 2020].

2. Expedited Programs for Serious Conditions (Guidance Document). Silver Spring (MD): Food and Drug Administration. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-serious-conditions-drugs-and-biologics [cited September 15, 2020].

3. Electronic Common Technical Document (eCTD). Silver Spring (MD): Food and Drug Administration. Available from https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/electronic-common-technical-document-ectd [cited September 15, 2020].

4. Assessment Aid. Silver Spring (MD): Food and Drug Administration. Available from https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid [cited September 15 2020].

5. Real-Time Oncology Review Pilot Program. Silver Spring (MD): Food and Drug Administration. Available from https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program [cited September 15 2020].

6. de Claro RA, Gao JJ, Kim T, Kluetz PG, Theoret MT, Beaver JA, Pazdur R. U.S. Food and Drug Administration: Initial Experience with the Real-Time Oncology Review Program. Clin Cancer Res. August 19, 2020 DOI: 10.1158/1078-0432.CCR-20-2220. Online ahead of print.

7. The Centre for Innovation in Regulatory Science (CIRS). R&D Briefing 77 New drug approvals in six major authorities 2010-2019: Focus on Facilitated Regulatory Pathways and Internationalisation. Available from https://cirsci.org/wp-content/uploads/2020/06/CIRS-RD-Briefing-77-6-agencies.pdf [cited September 15, 2020].

317 **Tables and Figures:**

318 Table 1. Types of Project Orbis Submission Plans

Project Orbis Type		**Sharing of FDA Reviews**	**Multi-country meetings**	**Concurrent review with FDA**	**Plan for concurrent action with FDA**
Type A	Regular	Yes	Yes	Yes	Possible
Type B	Modified	Yes	Yes	Possible	No
Type C	Written Report Only	Yes	No	No	No

319

320 Table 2: Comparison of Time-to-Approval between FDA and Orbis Countries for Project Orbis
321 Marketing Applications

Median (range), in months	**US Food and Drug Administration**		**Orbis Countries**	
All applications	4.2 (0.9, 6.9)	N=18	4.4 (1.7, 6.8)	N=20
New molecular entities / New active substances	5.1 (3.9, 6.9)	N=6	5.9 (3.9, 6.8)	N=7
Supplements / Variations for new indications	3.6 (0.9, 6.0)	N=12	3.3 (1.7, 6.4)	N=13

Figure 1: Project Orbis Marketing Application Submissions and Approvals: Year One Experience. *Initial set of Orbis applications based on 21 FDA applications received from 12 Jun 2019 to 12 Jun 2020. Abbreviations: FDA, Food and Drug Administration (USA); TGA, Therapeutic Goods Administration (Australia); HC, Health Canada; SMC, Swiss Agency for Therapeutic Products (Swissmedic) (Switzerland); HSA, Health Sciences Authority (Singapore); ANVISA, Brazilian Health Regulatory Authority.

Figure 2: Gap Time between FDA and Orbis Submission and Approval Dates. Vertical bar represents the median, and interval represents the interquartile range. Abbreviation: n.d., not determined

Glossary

AAid	Assessment Aid
ACSS	Australia, Canada, Singapore, and Switzerland Consortium
ANVISA	Brazilian Health Regulatory Agency
EMA	European Medicines Agency
FDA	Food and Drug Administration
HC	Health Canada
HSA	Health Sciences Authority (Singapore)
NAS	New Active Substance
NME	New Molecular Entity
OCE	Oncology Center of Excellence
POP	Project Orbis Partner(s)
POWG	Project Orbis Working Group
RHA	Regulatory Health Authority
SMC	Swissmedic
TGA	Therapeutic Goods Administration (Australia)

Figure 1:

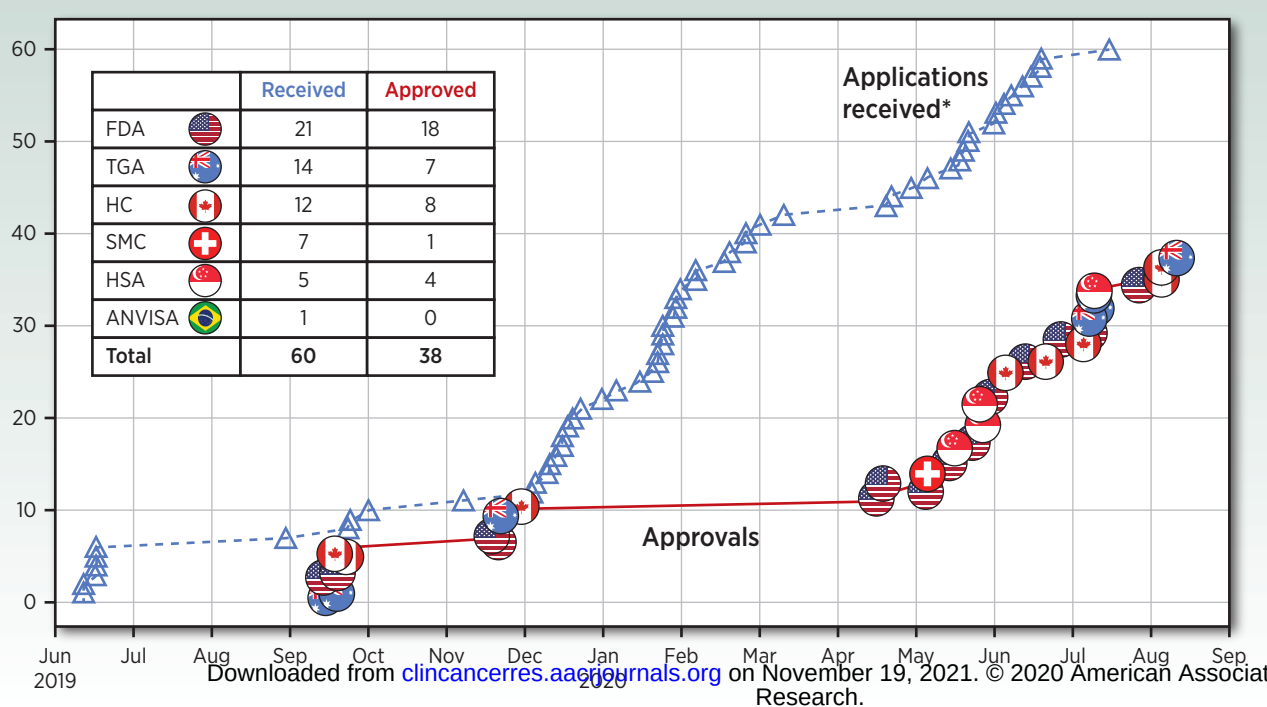
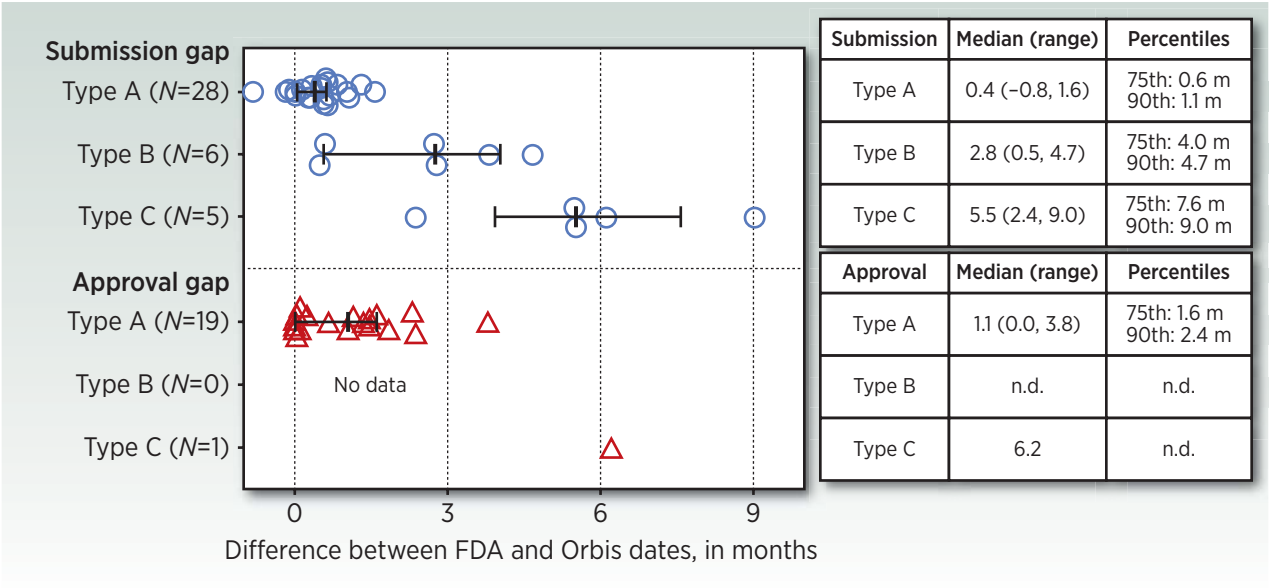


Figure 2:



Submission	Median (range)	Percentiles
Type A	0.4 (−0.8, 1.6)	75th: 0.6 m 90th: 1.1 m
Type B	2.8 (0.5, 4.7)	75th: 4.0 m 90th: 4.7 m
Type C	5.5 (2.4, 9.0)	75th: 7.6 m 90th: 9.0 m

Approval	Median (range)	Percentiles
Type A	1.1 (0.0, 3.8)	75th: 1.6 m 90th: 2.4 m
Type B	n.d.	n.d.
Type C	6.2	n.d.

AACR American Association for Cancer Research

Clinical Cancer Research

Project Orbis: Global Collaborative Review Program

R. Angelo de Claro, Dianne Spillman, Lauren Tesh Hotaki, et al.

Clin Cancer Res Published OnlineFirst October 9, 2020.