

1 **Perspectives in Regulatory Science and Policy**

2 **Title: Project Orbis: Global Collaborative Review Program**

3 **Authors:** R. Angelo de Claro^{1,2}, Dianne Spillman¹, Lauren Tesh Hotaki¹, Michael Shum³, Laila
4 Sofia Mouawad⁴, Gustavo Mendes Lima Santos⁴, Kelly Robinson⁵, Melissa Hunt⁵, Caroline
5 Healy⁵, Agnes Chan⁶, Yee Hoo Looi⁶, Clare Rodrigues⁶, Ulrich-Peter Rohr⁷, Chantal Walther⁷,
6 Richard Pazdur^{1,2}

7 **Running Title:** Year One Experience

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

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

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

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

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

19 **Abstract:**

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

39

40 **Introduction**

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

45
46 RHA partners at the program start in May 2019 were the Therapeutic Goods Administration
47 (TGA) and Health Canada (HC), the RHA of Australia and Canada, respectively. In December
48 2019, Project Orbis expanded to include the RHA from Singapore and Switzerland, which are
49 Health Sciences Authority (HSA) and Swissmedic (SMC), respectively. In May 2020, Brazil's RHA,
50 Brazilian Health Regulatory Agency (ANVISA) joined Project Orbis.

51
52 Prior to Project Orbis, the RHA of Australia, Canada, Singapore, and Switzerland (ACSS) had
53 formed the ACSS Consortium in 2007. The ACSS Generics and New Active Substance (NAS)
54 Working Groups established a work-sharing initiative to handle the increasing workload and
55 complexity of marketing applications (1). FDA leveraged the existing collaboration within ACSS
56 for the selection of the initial countries to participate under Project Orbis.

57
58 Project Orbis builds on the existing international regulatory collaboration for oncology drug
59 development between FDA and counterpart RHA (date of establishment of FDA oncology
60 collaboration) from the European Union (2004), Canada (2010), Japan (2014), Australia (2014),
61 and Switzerland (2016). Prior to Project Orbis, the FDA international collaboration primarily

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

68

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

74

75 **Project Orbis Implementation**

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

81

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

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

94

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

100

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

106

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

115

116 There are several types of Project Orbis submissions that have evolved and are dependent on
117 the timelines between FDA and the POP (Table 1). During the initial implementation of the
118 program, marketing applications were submitted concurrently or near-concurrently (within 30
119 days) to FDA and the POP. These applications are termed as Type A Orbis (Regular Orbis) and
120 requires submission of the marketing applications to the participating countries within 30 days
121 of the FDA submission. Type A Orbis allows for maximal collaboration during the review phase.
122 Marketing applications submitted through Project Orbis but associated with expected delays of
123 > 30 days on the application submission and/or regulatory action > 3 months of the FDA action
124 date are termed as Type B Orbis (Modified Orbis). Finally, for applications where FDA already
125 took regulatory action, there is Type C Orbis (Written Report Only Orbis) which allows FDA to
126 share their completed review documents with the POP.

127

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

141

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

150

151 **Project Orbis: First Year Experience**

152 The results below represent the Project Orbis workload based on the first-year set of 21
153 oncology marketing applications received by FDA from June 12, 2019 to June 12, 2020.

154 Regulatory actions from the POWG (FDA + POP) and the corresponding 39 marketing
155 applications received by the POP through August 15, 2020 are included in the analyses.

156

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

165

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

169

170 All of the applications selected by FDA for Project Orbis met criteria for FDA priority review.

171 Additional FDA Expedited Programs such as Breakthrough Therapy Designation and the Real-

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

176
177 Project Orbis received 17 new molecular entity (NME), also known as new active substance
178 (NAS) submissions, corresponding to 6 unique NME/NAS products in the first year of the
179 program. Project Orbis NME/NAS workload comprised 28% of the total workload. For NME/NAS
180 applications, Project Orbis also implemented the use of a CMC (Chemistry, Manufacturing, and
181 Controls) version of the AAid in addition to the multi-disciplinary AAid.

182
183 Major oncology disease categories were represented in the Orbis submissions, including solid
184 tumor and hematologic malignancy indications. The most common oncology indications in
185 Project Orbis (number of application submissions) were non-small cell lung cancer (N=10),
186 chronic lymphocytic leukemia (N=10), acute myeloid leukemia (N=6), endometrial cancer (N=6),
187 breast cancer (N=5), and hepatocellular cancer (N=5).

188
189 Comparison of the submission and approval dates for FDA and the POP showed minimal lag
190 times (Figure 2) between the FDA and the POP for Type A applications. For the 39 Orbis
191 applications submitted to the POP, the median time gap between FDA and POP submission
192 dates was 0.6 months with a range of -0.8 to 9.0 months. The breakdown according to Orbis
193 Type is shown in Figure 2, with a median submission time gap of 0.4, 2.7, and 5.5 months for

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

196

197 The median time gap for approvals for Type A applications between FDA and the POP was
198 1.1 months, with 90% of the approvals conducted within 2.4 months of the FDA approval date.

199 Time-to-approval analyses showed similar metrics between FDA and the POP overall and
200 separated by type of application (NME/NAS versus supplement/variation) (Table 2).

201

202 **Discussion**

203 Through close collaboration between the RHA, Project Orbis demonstrates that the delay in
204 marketing application submission and approval in Orbis countries can significantly be reduced,
205 with several applications achieving parity or near-parity with FDA timelines. Analyses of
206 NME/NAS marketing applications from 2015-2019 noted a median overall gap time (submission
207 and approval) of 6.4, 8.4, and 9.5 months for HC, TGA, and SMC compared to FDA (7). For Type
208 A applications under Project Orbis, the median overall gap time (submission and approval) was
209 1.5 months, with a 90th percentile of 2.8 months between FDA and the POP. This increased
210 efficiency was achieved using the available resources within each RHA.

211

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

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

221

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

227

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

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

239

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

248

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

255

256 **Future Directions**

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

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

263
264 Possible areas for expansion for Project Orbis involve participation of other countries, and
265 handling of more complex applications, such as those that involve companion diagnostic
266 devices or advanced therapy products such as cellular and gene therapies. It would be
267 important to be aware of an inflection point where a critical mass of participating countries or
268 applications is reached that reduces the review efficiency achieved with Project Orbis. Likewise,
269 the regulatory framework for in vitro diagnostic devices and advanced therapies would add to
270 the complexity of Project Orbis review.

271
272 Project Orbis demonstrates that global regulatory collaboration is attainable and can deliver
273 faster access to new therapies for patients with cancer across multiple countries. Reduction of
274 the regulatory approval gap through Project Orbis represents an initial major step for
275 expediting patient access. A possible future direction for Project Orbis would be earlier
276 interactions with health technology assessment bodies that determine coverage decisions.

277
278 Extension of the collaborative efforts to other aspects of oncology drug development, including
279 clinical trial endpoints, trial designs, enrollment criteria, and postmarketing surveillance can
280 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.

283

284 **References:**

285

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

290

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

295

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

299

300 4. Assessment Aid. Silver Spring (MD): Food and Drug Administration. Available from
301 <https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid> [cited September
302 15 2020].

303

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

307

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

311

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

316

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 |

322 Figure 1: Project Orbis Marketing Application Submissions and Approvals: Year One Experience. *Initial set of Orbis applications based on
323 21 FDA applications received from 12 Jun 2019 to 12 Jun 2020. Abbreviations: FDA, Food and Drug Administration (USA); TGA,
324 Therapeutic Goods Administration (Australia); HC, Health Canada; SMC, Swiss Agency for Therapeutic Products (Swissmedic)
325 (Switzerland); HSA, Health Sciences Authority (Singapore); ANVISA, Brazilian Health Regulatory Authority.
326

327 Figure 2: Gap Time between FDA and Orbis Submission and Approval Dates. Vertical bar represents the median, and interval
328 represents the interquartile range. Abbreviation: n.d., not determined
329
330

331 **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) |

332

Figure 1:

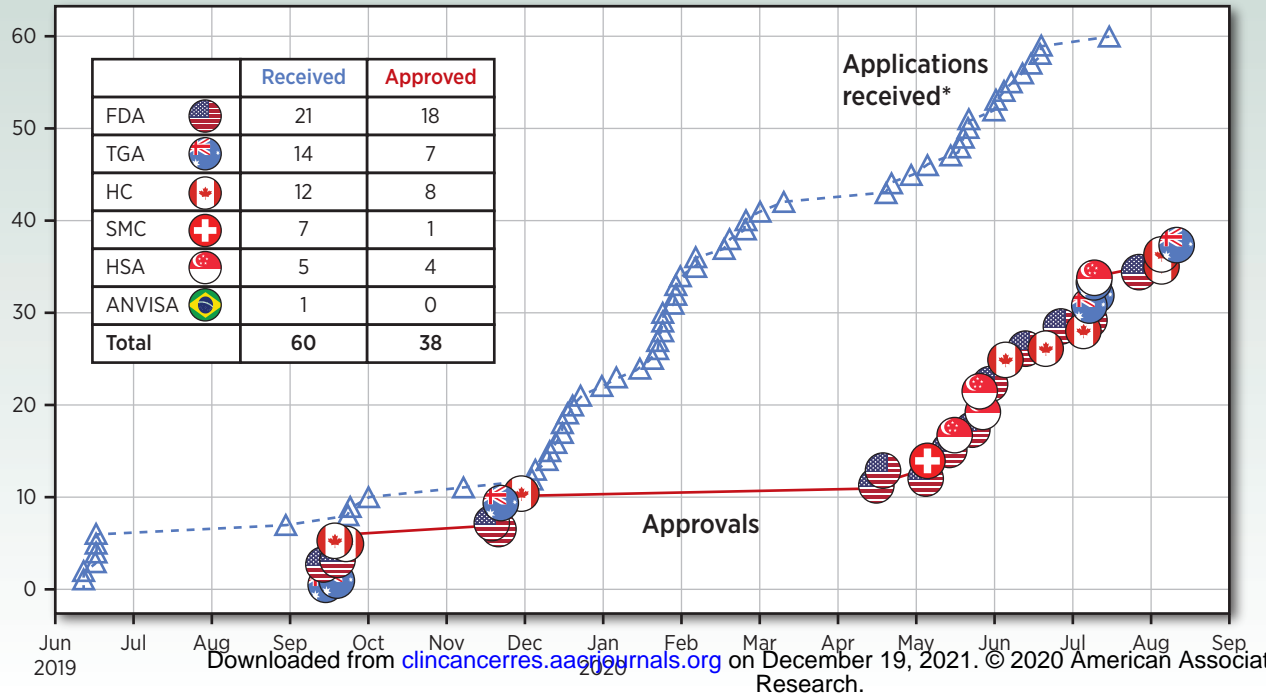
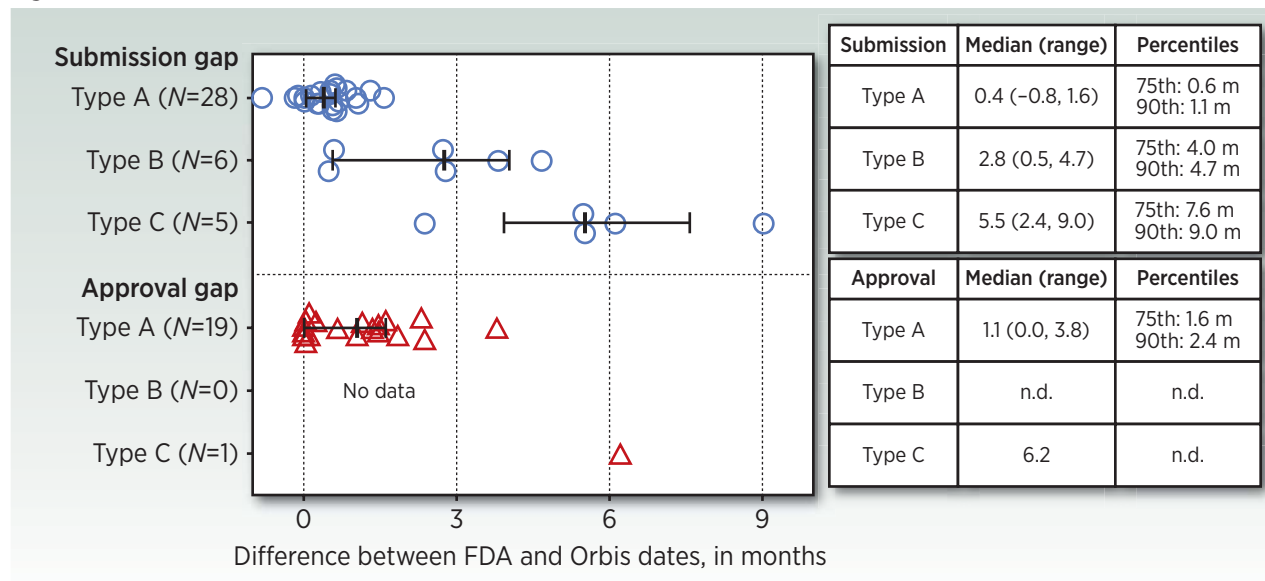


Figure 2:



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.

| | |
|--------------------------|--|
| Updated version | Access the most recent version of this article at: doi: 10.1158/1078-0432.CCR-20-3292 |
| Author Manuscript | Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited. |

E-mail alerts [Sign up to receive free email-alerts](#) related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, use this link <http://clincancerres.aacrjournals.org/content/early/2020/10/09/1078-0432.CCR-20-3292>. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.