REGULATORY FOCUS

Project Orbis: Maximizing patient access to new medicines

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To ensure equitable access to new medicines for all patients, drug manufacturers aim to register new products in as many countries as possible. Project Orbis, an initiative of the FDA Oncology Center of Excellence (OCE), is a pilot program that provides applicants with a framework for concurrent submission and review of oncology products among international partners to allow earlier registration in countries outside of the US. This article summarizes Genentech's experience with the pilot from November 2019 to December 2020.

Introduction

To ensure equitable access to new medicines for all patients, drug manufacturers aim to register new products in as many countries as possible, as quickly as possible. Project Orbis, an initiative of the US Food and Drug Administration's (FDA's) Oncology Center of Excellence (OCE), is a pilot program that provides applicants with a framework for concurrent submission and review of oncology products among international partners to allow earlier registration in countries outside of the US. The pilot was originally aimed at the review of supplemental applications, however, it has since expanded to include

the review of new drug applications (NDAs) and biologic license applications (BLAs). To date, several health authorities have participated in the pilot, with much success, and the coordination of efforts between participating countries allows these much-needed treatments to reach patients sooner.

To determine if a study is eligible for participation in this program, applicants should assess the complexity of the study data; whether there is the potential to participate in other FDA pilots in parallel; the availability of internal resources; and the technology needed to conduct a simultaneous review across jurisdictions. With these key components in place, applicants improve their chances of a smooth review process. Furthermore, whether health authorities (HAs) participate in Project Orbis also depends on a number of factors, including capacity for review of the data and an interest in the particular indication sought by the applicant. It is important to keep in mind that as this is a pilot program, the countries and applicants participating in Project Orbis are learning with each subsequent review, and therefore, the requirements and processes continue to evolve. The purpose of this article is to share an overview and evolution of Project Orbis in addition to Genentech's experience with the program from November 2019 to December 2020.

Background

In 2004, the FDA's Office of Oncologic Diseases (OOD; formerly Office of Hematology and Oncology Products) began holding regular teleconferences under a confidentiality agreement with other regulatory agencies to allow for the exchange of information and collaboration on specific topics related to applications under review. Over time, this has led to increased interactions between HAs internationally and currently, the OOD holds a monthly teleconference with Australia's Therapeutic Goods Administration (TGA), Health Canada, the European Medicines Agency, Japan's Pharmaceuticals and Medical Devices Agency (PMDA), and Switzerland's Swissmedic. In addition, the FDA and China's National Medical Products Administration have initiated a quarterly meeting to discuss non–product-specific regulatory issues facing worldwide drug development.[1]

Project Orbis is an initiative of the FDA's OCE, which provides a framework for concurrent submission and review of NDAs/BLAs and supplemental applications for high-impact oncology products among international partners that typically meet the criteria for FDA's priority review. The intent of this collaboration is to allow equitable access to life-saving medicine for all patients with cancer, regardless of geographical location and whether the product has received FDA approval.[2]

To date, several HAs have participated in the pilot with much success, and the coordination of efforts between participating countries allows these much-needed treatments to reach patients sooner. At the outset, the scope of the pilot included only the review of supplemental applications, however, the FDA expanded the program in December 2019, to include the review of NDAs and BLAs.

Early engagement

Once data is available to support an application, sponsors submit a formal request to the FDA to participate in Project Orbis in advance of the license application submission. If the FDA determines the sponsor's application qualifies for the program, the agency will inform the applicant and invite them to meet to discuss the timelines and specifics of the review.

Project Orbis submission plans

Several types of Project Orbis submission plans have evolved over the course of the pilot (**Table 1**). These are defined by the time between the start of the review of the application by the FDA and the start of the review by the participating HAs.[3]

During the initial implementation of the program, marketing applications were submitted concurrently or near-concurrently (within 30 days) to FDA and the participating HAs. These applications are termed as Type A Orbis (Regular Orbis) and require the submission of the marketing applications to the participating HAs within 30 days of the FDA submission. Type A Orbis allows for maximal collaboration during the review phase.[3]

Marketing applications submitted through Project Orbis, but associated with expected delays of more than 30 days on the application submission and/or regulatory action of more than 3 months of the FDA action date, are termed as Type B Orbis (Modified Orbis).[3]

Type A or B Orbis submissions include the additional requirement of the assessment aid.[4] The assessment aid is a tool that was originally intended to streamline the FDA review to make it more efficient and decrease the administrative burden for the FDA. This document, now an integral tool supporting Project Orbis, serves as the core assessment document for discussions between HAs. While the assessment aid can accommodate the differences in assessment from the participating HAs, use of the document as an evaluation tool remains under the discretion of the individual HAs.[3]

For applications in which the FDA has already taken regulatory action, there is the Type C Orbis (Written Report Only Orbis Plan), which allows the agency to share its completed review documents with the participating HAs to facilitate the review of the application in that country.[3]

TABLE 1 **Types of Project Orbis submission plans**

Project Orbis type	Sharing of FDA reviews	Multicountry meetings	Concurrent review with FDA	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

Project Orbis review process

The review process differs depending on the type of Project Orbis submission plan. For Type A and certain Type B applications, the FDA schedules and coordinates teleconferences to discuss various aspects of the application. These include a kick-off meeting and multiple discipline-specific meetings. For Type B applications, the number of multicountry meetings depends on the length of time between the start of the FDA review and submission of the application to the participating HAs. The aforementioned meetings do not occur for Type C applications because the FDA has already completed the review.[3]

Each participating HA remains completely independent in its review and regulatory decision-making, which ensures continued adherence to its country-specific laws and regulations. As a result, there may be differences in the approval or rejection of an application, the type of approval, timing of the final decision, wording of the approved indication and general labeling content, as well as differences in potential postmarketing requirements.[3]

While the official Project Orbis review timelines are aligned with the established review timelines of each HA, the FDA has indicated there has been a reduction in time to approval for both the FDA and participating Project Orbis HAs for new molecular entities and supplement applications (**Table 2**).

For example, for the first Project Orbis action, on 17 September 2019, Merck saw a 3-month decrease in the time to obtain FDA approval for Lenvima (lenvatinib) in combination with Keytruda (pembrolizumab) for the treatment of patients with advanced endometrial carcinoma through the coordinated review in conjunction with Australia's TGA and Health Canada.

Applicants must keep this autonomy in mind as they move through the review process understanding that coordinated participation in Project Orbis does not necessarily yield simultaneous and identical approvals across the participating HAs.

TABLE 2 Comparison of time-to-approval between FDA and Orbis countries[a] for Project Orbis marketing applications[3]

Application type	Median (range), in months [Number of applications]	
	FDA	Orbis countries
All applications	4.2 (0.9, 6.9) [18]	4.4 (1.7, 6.8) [20]
New molecular entities/new active substances	5.1 (3.9, 6.9) [6]	5.9 (3.9, 6.8) [7]
Supplements/variations for new indications	3.6 (0.9, 6.0) [12]	3.3 (1.7, 6.4) [13]

[a]Project Orbis partners include the regulatory health authorities of Australia, Brazil, Canada, Singapore, Switzerland, and the United Kingdom. Israel and Japan have participated as observers.

Considerations for planning a Project Orbis submission

Though the FDA reaches out to potential candidates it considers eligible for the program, applicants can make an internal assessment ahead of time whether an application is eligible for participation. An early assessment allows companies to better plan resources and prioritize activities if their applications are selected for the pilot.

Assessment aid

The assessment aid[4] is an additional document that is required when following the Type A or B submission plan. Although primarily an FDA pilot, this document is also shared with participating HAs and has become an integral tool to support Project Orbis. Its objective is to focus the review on the most critical aspects of the dossier to increase review efficiency and consistency and decrease review time. The FDA has encouraged applicants to keep the document as scientific, factual, and technical as possible, without the inclusion of any promotional or interpretive language, to reduce the need to seek clarification from the applicant throughout the review. To this end, the agency has created an assessment aid template for sponsors and has provided guidance for completing this document, including examples of past assessment aids on the FDA OCE website.[4] Applicants should consider what additional time and resources will be needed to prepare this document and incorporate these details into the overall submission plan.

Health authority capabilities

When planning the review of an application under Project Orbis, the FDA coordinates the other reviewers by reaching out to regulatory HAs to confirm interest and availability. Regulatory HAs have the opportunity to either be active participants or observers. The FDA then confirms the global submission plan with the sponsor, which has the opportunity to select the number of regulatory HAs involved in the review.[3]

Considerations that influence whether different HAs participate in the pilot include the requirement to have a confidentiality agreement with the FDA and the other participating HAs. Regulatory HAs must also be able to accept dossiers in English, because it removes the additional time and logistics needed for the translation of dossiers and responses to HA questions. They should also have the capacity to participate in cross-HA review discussions in English.

It is important to consider that HA technological capabilities vary and need to be taken into account during the planning of document publishing and in anticipating review timelines. For example, some HAs do not have an electronic common technical document (eCTD) portal and rely on non-eCTD electronic submissions. Furthermore, resourcing capabilities differ between HAs, which is an important consideration when deciding whether they will participate in the pilot.

Current Project Orbis partners include the regulatory HAs of Australia (TGA), Brazil (ANVISA), Canada (Health Canada), Singapore (HSA), Switzerland

(Swissmedic), and the UK (MHRA). Israel (Ministry of Health) and Japan (PMDA) have also participated as observers.

Impact of Project Orbis on other pilots

Applicants can elect to participate in other programs, such as real-time oncology review (RTOR), in parallel with Project Orbis, if they are invited to do so by the FDA. The qualification criteria for Project Orbis and RTOR are very similar, making it possible for marketing applications and supplements to qualify for both pilots. Applicants should consider whether the goals and aims of the programs align, as well as whether there are any disadvantages to participating in multiple pilots simultaneously.

If an application qualifies for both the RTOR and Project Orbis pilots, it is important to consider that the RTOR pilot is managed by the FDA alone. Other countries participating in the Project Orbis pilot may not have adequate resourcing and processes in place to adhere to the same review timelines, which may lead to a difference in review and approval timelines by the other participating HAs relative to the FDA.

Data complexity

To achieve the goal of the pilot, which is to provide patients with earlier access to treatments in countries outside of the US, participating HAs are allowed access to data not required by their regulatory frameworks for evaluating a medicine's benefit-risk profile. As such, applicants must determine if their data allows for efficient review by multiple HAs. Factors such as a complex study design or the addition of a diagnostic tool may make the application less desirable for the pilot at this stage.

To assess eligibility, applicants should consider the following:

- All applications are expected to meet the criteria for priority review. These products should offer significant improvements in the safety or effectiveness, diagnosis, or prevention of serious conditions when compared with standard of care;
- Drugs that are likely to demonstrate substantial improvements over available therapy, which may include drugs previously granted breakthrough therapy designation;
- Straightforward study designs, as determined by the review division at FDA and the OCE; and
- Endpoints that can be easily interpreted (e.g., overall survival in a randomized trial).

Resourcing

Applicants need to determine if there are adequate resources within their organization at the global and local affiliate levels to handle simultaneous review of the dossier and label negotiations, as well as to support presubmission meetings across multiple jurisdictions, for Type A and B submission plans. It is also important that regional affiliates have enough resources/capacity to handle a simultaneous submission to their respective HAs and a coordinated review with FDA. Early engagement with regional affiliates may help mitigate this

consideration and ensure alignment with the global regulatory strategy prior to regional HA interactions. As part of the Project Orbis process itself, each HA may request courtesy copies of the Information Requests issued by each country participating in the review, as well as the responses issued to these requests. This can be quite resource intensive as it requires the coordination of the submission of these documents to different regions. Additional resources to prepare the assessment aid and participate in parallel pilots should also be considered.

Labeling

Though the reviews are coordinated across participating countries, regional labels still need to be produced and negotiated with each HA individually. Companies preparing for review under Project Orbis should consider the differences in regional labeling requirements, such as frequency cut-offs for serious adverse events, early in the process to ensure all of the data needed is available. It is also worth noting that participating in Project Orbis does not always yield fully harmonized labels.

Looking to the future

Randomized clinical trials continue to be the backbone of the registration of medicinal products worldwide. In this global environment, it is commonplace for these pivotal trials to be conducted internationally and the strategy implemented by sponsors to investigate the safety and effectiveness of oncology products plays a vital role in the approval of these products across multiple markets. As Project Orbis and other types of coordinated review procedures, such as work-sharing under the Access Consortium (previously referred to as "ACSS")[5] and ZaZiBoNa[6] in Southern Africa (comprised of Zambia, Zimbabawe, Botswana, and Namibia) become more routine, it may be beneficial to establish new global standards to optimize clinical trial design to make them more amenable to simultaneous international review.

As Project Orbis moves forward and the process becomes more streamlined, the FDA may seek to expand the scope to include the participation of additional countries and the handling of more complex applications, such as those that involve companion diagnostic devices or advanced therapy products such as cellular and gene therapies. Regional affiliates continue to play a key role in shaping and advancing the scale of these coordinated reviews by working with their local health authorities to overcome barriers and seize opportunities to participate. By working together, we can ensure faster delivery of medicines to patients regardless of where they are across the globe.

Abbreviations

BLA, biologic license application; **eCTD,** electronic common technical document; **FDA,** [US] Food and Drug Administration; **HA,** health authority; **NDA,** new drug application; **OCE,** Oncology Center of Excellence; **OOD,** Office of Oncologic Diseases; **RTOR,** real-time oncology review.

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