MEDTECH INSIGHT
CITELINE COMMERCIAL

13 Feb 2023 | **News**

US FDA Eyes Project Orbis-Type Approach For Cell And Gene Therapies

by Sue Sutter

A process in which the FDA coordinates reviews with other regulators would allow for better leveraging of global patient populations with ultra-rare diseases and attract more commercial interest in a given disease area, CBER's Peter Marks tells the Biopharma Congress. The biologics center also looks to apply the philosophy underlying the Real-Time Oncology Review program.

The US Food and Drug Administration is eyeing potential adoption of a Project Orbis-type approach for cell and gene therapies to treat rare diseases.

A process where the FDA can coordinate reviews with other regulators would allow for better leveraging of global patient populations with ultra-rare diseases and attract more commercial interest in development for a particular disease area, Center for Biologics Evaluation and Research Director Peter Marks said at the Prevision Policy/Friends of Cancer Research Biopharma Congress meeting on 13 February.

"This concept that FDA can serve as almost a reference regulatory authority for other countries that might approve things at the same time or near same time [the Oncology Center of Excellence's Project Orbis], I think is really important," Marks said. "A lot of these gene therapies have such small populations that are applicable to them in the United States that if we could expand those markets into other high-income countries, it would attract more developers, which would allow more diseases to be covered."

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"Especially when you think about some of the rarer diseases," Marks continued. "The US might have 20 patients, but that means EU probably has 30 or 40 patients, Japan might have another 10 patients, and some other high-income countries, put them together and you get to this magic 100 to 200 patients a year, which is where commercial viability starts to become real."

68 Orbis Approvals

Project Orbis provides a framework for concurrent submission and review of oncology products among international partners.

In September 2019, the FDA, Australian Therapeutic Goods Administration and Health Canada partnered on the first approval under Orbis, for *Eisai Co., Ltd.*'s kinase inhibitor Lenvima (lenvatinib) in combination with *Merck & Co., Inc.*'s PD-1 inhibitor Keytruda (pembrolizumab) for the treatment of certain patients with advanced endometrial carcinoma. (Also see "*US FDA's Project Orbis Could Streamline Global Clinical Trials In Cancer*" - Pink Sheet, 17 Sep, 2019.)

The initiative has since gained additional partners, including regulatory authorities in Brazil, Israel, Singapore, Switzerland and the UK.

The FDA's website lists 68 product approvals in the US under Orbis. Most of these products also either have been approved by the partner countries, or application reviews are ongoing.

While it is important for CBER to learn what it can from Project Orbis, Marks said he wants to take that effort one step further for rare diseases, creating something akin to the World Health Organization's prequalification process for vaccines.

"Basically WHO says this vaccine has been licensed in a reference country. It's good enough for us, should be good enough for you," Marks said. "The idea here is could we do that for gene therapy so that even middle- to low-income countries could potentially make use of these approvals in their countries?"

This is important, Marks said, “because for some gene therapies the only way people will ever get treatment in low-income countries is if they get a gene therapy, because those countries cannot afford supportive care. For instance, a disease like beta thalassemia major, which requires transfusions, iron chelation and close monitoring, it's not realistic in a low- and middle-income country to see that really be successful. But a gene therapy that's one-and-done could be.”

“Now granted, there's this big upfront cost,” Marks said, “but there may be ways to deal with that.”

Marks previously has spoken about discussions with WHO to create a regulatory framework that would enable access to cell and gene therapies in low- and middle-income countries, as well as efforts to develop better convergence with other large, global regulators for gene therapies in very small patient populations. (Also see "*US FDA Pursuing Two-Track Approach To Regulatory Convergence For Cell and Gene Therapies*" - Pink Sheet, 24 Jun, 2022.)

Speaking during a separate session of the Biopharma Congress, Office of Tissues and Advanced Therapies Director Wilson Bryan said Orbis is his favorite of the OCE projects, which he described as “pilot programs that they work out the bugs before they come to us.”

Project Orbis “really helps … patients around the world,” Bryan said. “There's no question in my mind that Project Orbis at some point, with some application, will come to CBER.”

Applying An RTOR Philosophy

Marks also is looking to leverage the philosophy underlying another OCE initiative, Real-Time Oncology Review, for cell and gene therapies to treat rare diseases.

CBER is getting ready to pilot a program that extends to the rare disease space the type of the extensive interactions and intensive communications that characterized the development of COVID-19 vaccines under Operation Warp Speed. (Also see "*Operation Warp Speed For Rare Diseases? US FDA Is Considering Pilot Programs*" - Pink Sheet, 29 Jun, 2022.)

“I think the goal is to take products that already have shown some promise in the rare disease space for diseases that don't have alternatives,” Marks said. “The idea here is if we're going to do a pilot, let's do it in a place where we may make a real difference for patients. And then take these products – they may have breakthrough designation, they may have regenerative medicine advanced therapy designation – but they've at least shown that they have promise and they're in the process of making their way through development.”

The pilot would give sponsors of such products “the opportunity to have not just conversations around chemistry, manufacturing and controls, which we have a pilot for, but allow the clinical development to happen with constant communication, and constant sharing” of study results,

"allowing things to speed up."

The concept underlying OCE's RTOR program is that by the time a trial is completed, it does not take long for the agency to see the results, even before a new drug application or biologics application submission has occurred, Marks said. "I think that's the idea here, that we can try to move things as fast as possible, remove delays, and avoid some of the issues that have occurred."

Marks said the goal of the rare disease pilot would be to address hiccups in cell and gene therapy development programs earlier.

"If those conversations can occur in real time, we'll hopefully resolve those rather than wait for kind of okay, trial is over now. And oops, we realized that there was something that should have been done differently, something that should have been collected, that six months into the trial maybe could have been remediated. So just the hypothetical example of what we might try."

RTOR facilitates earlier submission of top-line efficacy and safety results, prior to the submission of the complete application, to support an earlier start to the FDA's evaluation of an oncology drug application.

> ***"We have to find things in cell and gene therapy that aren't complicated, that don't have great manufacturing issues." – FDA's Wilson Bryan***

Original NDAs and BLAs, as well as supplemental applications, may be eligible for RTOR. However, such products must be likely to demonstrate substantial improvements over available therapy or meet criteria for expedited programs. In addition, development programs must have straightforward study designs and endpoints that can be easily interpreted.

A July 2022 draft guidance on RTOR states the program "may not be suitable for certain biological products, such as cell and gene therapies, for which complex manufacturing and product characteristics need to be considered in evaluating the safety and efficacy of the product." (Also see "*US FDA's Real-Time Oncology Review Program Is No Guarantee For Early Approval*" - Pink Sheet, 27 Jul, 2022.)

When asked about the prospects for extending the RTOR philosophy to CBER, OTAT's Bryan noted the complicated nature of gene and cell therapies could pose challenges.

With OCE's RTOR program, "there's a bit of cherry picking" in that the most complicated products are excluded, he said.

"You don't put the ones that have CMC manufacturing issues into Real-Time Oncology Review. Now maybe that will evolve. So we have to find things in cell and gene therapy that aren't complicated, that don't have great manufacturing issues. And I think we'll be doing that with some efficacy supplements, but probably not original BLAs for some time."

Bryan will retire from the agency by the end of March, shortly after OTAT is scheduled to reorganize into a "super office" that will be renamed the Office of Therapeutic Products. (Also see "*FDA's Cell, Gene Therapy Office Head Wilson Bryan Set To Retire*" - Pink Sheet, 30 Jan, 2023.) CBER Deputy Director Celia Witten will take over as acting office head. (Also see "*The Risk-Reward Of US FDA Leadership Running Offices Below Them*" - Pink Sheet, 9 Feb, 2023.)

Given his impending departure, Bryan declined to say when CBER might start implementing its own versions of Project Orbis or RTOR for cell and gene therapies.

"Part of my responsibility as someone who's leaving is not to try to put a burden on the people who have stayed in house. So I'm not going to say a timeline for when Orbis or Real-Time Oncology Review or any of the other wonderful things that are going on in the [Oncology] Center of Excellence will be implemented in CBER."