Next-Gen Cell Therapies Bedeviled by Regulatory Murkiness on Product Characterization, Manufacturing

At a recent Friends of Cancer Research meeting, drugmakers and regulators said communication has improved on cell therapy development programs but acknowledged persistent challenges.

By Caroline Hopkins

DRUGMAKERS working with the US Food and Drug Administration to bring more effective, efficient, and less toxic cancer cell therapies to market are finding that while the agency has gotten better at communicating with industry, a lack of regulatory clarity on manufacturing processes and product characterization is still thwarting their development programs.

In a roundtable hosted by the nonprofit Friends of Cancer Research in March, stakeholders from the US Food and Drug Administration, academia, and industry discussed the regulatory landscape for "next-generation" cell therapies, specifically, new iterations of CAR T-cell therapies with which the field now has some experience. With six FDA-approved CAR T-cell cancer therapies on the market, drugmakers and regulators have a better idea of the framework needed to bring safe and effective cell therapies to market than they

did several years ago. But manufacturing and product characterization remain murky topics of interaction between regulators and drugmakers.

The sponsors of these next-generation products want patients with solid and hematologic cancers to have more durable responses to these therapies. They want to develop these drugs more efficiently, and deliver them to patients faster, at a lower cost, and with fewer toxicities.

Toward that end, drugmakers are developing next-generation cell therapies that target new antigens on cells. Some firms are diverging from the lentiviral gene editing technique typical of currently marketed cell therapies. Others are using different cell types as autologous or allogeneic starting material. And most of these newer therapies boast a shorter turnaround time than the several weeks it currently takes to harvest a patient's T cells, engineer them to express a specific antigen-targeting chimeric antigen receptor, expand those cells *ex vivo*, and then reinfuse them into the patient.

Novartis, Bristol Myers Squibb, and Gilead Sciences subsidiary Kite Pharma are among the biggest companies selling cancer cell therapies and all are working on newer iterations. Gilead, for example, which markets the CD19-directed autologous CAR T-cell therapies Yescarta (axicabtagene ciloleucel) and Tecartus (brexucabtagene autoleucel), decided last year to buy Tmunity Therapeutics, a next-generation cell therapy firm with a "rapid" manufacturing platform.

Novartis, which brought to market the first FDA-approved CAR T-cell therapy, Kymriah (tisagenlecleucel), unveiled a new platform, dubbed T-Charge, two years ago, hoping to use it to reduce cell culture time outside of the body. The first product Novartis developed with this platform is an autologous CD19-directed CAR T-cell therapy, dubbed YTB323. While Novartis is studying YTB323 as a treatment for diffuse large B-cell lymphoma, the same setting that Kymriah is approved for, the next-generation product is distinct from the marketed treatment in that it involves different manufacturing and engineering approaches.

'Building an avenue" to second-generation therapies

At the March Friends of Cancer Research meeting, which was the first of two planned meetings, experts in the field flagged areas of regulation that still need more clarity as drugmakers advance next-generation therapies. For example, drugmakers must grapple with the fact that a manufacturing tweak made to a product – say, a shift in processes meant to speed up turnaround time – could, in the FDA's eyes, constitute an entirely new product. This poses challenges for sponsors and regulators, especially if the manufacturing changes after the product has already entered the FDA review process.

"As we've seen chimeric antigen receptor T cells and other cellular therapies advance, the bottlenecks in development have to do with manufacturing," Peter Marks, the director of the Center for Biologics Evaluation and Research (CBER), said at the meeting. "We've seen the challenges that can occur when the transition to commercially viable processes is later than it should be in terms of delaying products coming to market."

Marks urged drugmakers, especially those that want to use new manufacturing processes for commercial-scale production, to begin pursuing regulatory approval for these processes early in drug development. "Sometimes, it just seems like that transition is happening later than it should," he said.

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For drugmakers who already have earlier-generation therapies approved, the experts at the meeting discussed how some data on the marketed therapies could inform regulation of the next-generation products. For instance, Jonathan Jazayeri, executive director of global regulatory affairs at Kite, shared how it was ultimately a manufacturing process change that differentiated the FDA-approved Tecartus from its otherwise similar predecessor Yescarta. The latter is approved for certain patients with large B-cell lymphoma, and the former is approved for certain patients with mantle cell lymphoma and B-cell precursor acute lymphoblastic leukemia.

Jazayeri pointed out that Yescarta and Tecartus target the same antigen and rely on the same vector for manufacturing. Both therapies involve harvesting patients' immune cells and engineering them to target CD19. "However, there are changes in the manufacturing process, and these changes in the manufacturing process have resulted in a change in the therapeutic effect," Jazayeri said.

For example, apheresis starting material for Yescarta comprises patients' lymphocytes, while Tecartus' starting material contains enriched T cells. Additionally, the media used for the T-cell activation step differs between the two products. Because these manufacturing tweaks resulted in a different therapeutic effect, Tecartus became a whole new product in accordance with the FDA's guidance on "sameness" for cell and gene therapies, Jazayeri said.

When Kite first submitted an investigational new drug application to study Yescarta using a new manufacturing process, which the company described as the "XLP process for axi-cel," the FDA determined that the manufacturing changes would produce a different enough product that Kite would have to submit a new biologics licensing application. That led to what is now Tecartus, a new drug sold under a different brand name and label.

Sponsors may find it painful to go back to square one with new iterations of marketed products, but Jazayeri highlighted the Yescarta-to-Tecartus transition as an example of how it's possible to work with FDA to extrapolate certain aspects of the older product to the newer one, such as safety data and starting doses.

"Every time we develop these next-generation assets, the approach that we have to start with is essentially square one, [but] this is an example of where a next-generation cell therapy product made it to clinic and was able to accelerate or skip some of these traditional first challenging steps," Jazayeri said. "[This] ultimately resulted in a successful program, which was able to deliver the treatment to patients sooner."

Gilead couldn't extrapolate everything, such as the analytical methods it used to test the long-term stability of Tecartus. Jazayeri further acknowledged that not all next-generation cell therapies will follow the Yescarta-to-Tecartus model, and that developing next-generation cell therapies can get more complicated when using a different vector to modify the cells or target a new cell-surface antigen. In these situations, there may be fewer opportunities to extrapolate data from an earlier product, he said, but "there may be relevance to carry through."

A consistent regulatory framework to help drugmakers understand when the data from a prior therapy can and can't be extrapolated to a newer version would be invaluable, Jazayeri urged. "If you don't build the avenue, cars aren't going to drive down," he said. "We need to discuss a framework that will allow more sponsors to share and discuss with the FDA opportunities for data extrapolation so that we can do this for more programs."

Regulators are also working to oversee cell therapy manufacturing more efficiently and consistently. For instance, Ingrid Markovic, a senior science advisor at FDA's CBER who

leads up chemistry, manufacturing, and controls (CMC) policy, said that on April 1, 2023, the agency will begin accepting applications for its new CMC readiness pilot program. This effort is meant to ensure "CMC can keep up the pace with clinical development" and improve communication between the FDA and sponsors, including having two CMC-specific meetings with each applicant. Markovic also pointed drugmakers to an FDA guidance issued in November detailing how industry can use an umbrella protocol to study multiple versions of a product in the same clinical trial.

"In [an umbrella protocol], the clinical, preclinical, and CMC information could be captured in the primary IND, and additional CMC information and preclinical information for the new product version could be provided in the secondary IND with necessary cross-referencing," she said. "The idea behind this is to help reduce administrative burden on both the sponsor and the FDA."

Product characterization, potency assays

When it comes to developing next-generation cell therapies, the stakeholders participating in the March discussion agreed that both regulators and industry have room to improve in terms of product characterization. The FDA requires drugmakers to clearly define what exactly a product is and to have a clear tool, or set of tools and assays, to ensure that the product consistently has these attributes when it's manufactured on a commercial scale. This has been a particular challenge for developers in the autologous cell therapy space, because it's not as straightforward to characterize a product that uses patient-specific starting material as it might be to characterize a small molecule product that's identical across batches.

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From industry's view, inconsistent regulatory feedback and guidelines on potency assays pose one of the biggest hurdles to bringing cell therapies to market. Recently, the sequencing company Mission Bio published results from a survey of 200 cell and gene therapy developers, in which 56 percent said they were dissatisfied with their approach to characterizing products; 40 percent said their characterization assays were not sufficient to determine consistent quality attributes of their products; and 81 percent said that better characterization of their products would reduce the risk of the FDA putting clinical holds on therapy trials. The survey findings bode well for Mission Bio, which offers product characterization techniques to cell therapy makers, but the data confirm that product characterization remains a trouble spot for next-generation therapies.

Julie Jadlowsky, the director of translational research operations at the University of Pennsylvania, said that cell therapy researchers at her institution have often received contradictory or discordant feedback from FDA on these assays. "Especially in things like potency or specificity, or even release testing, when we're submitting preclinical packages, we're getting a lot of divergent feedback, which is a little bit frustrating from our perspective because at that point, we're looking at potentially a clinical hold because we haven't addressed a particular issue that was never an issue in the past," she said. "It would be great if we could have more conversation or maybe develop frameworks or best practices that would help address" this inconsistency.

Marc Better, a consultant with the cell therapy and biologics CMC consulting firm Pharmefex, also pointed to product characterization and potency assays as an area that continues to bedevil cell therapy developers. "It's extremely important to have robust tools to understand what the product's biological properties really are and to be able to use those tools to guide development," Better said, noting this is all the more important with new iterations of existing products. "Analytical methods used for product release and for expanding characterization are essential to establish relationships between primary and secondary products."

Better's advice to sponsors echoes what regulators have long told companies making first-generation cell therapies: implement a potency assay strategy as early in the drug development cycle as possible.

As the field moves ahead, drugmakers, regulators, and researchers all hope that a growing body of data from past successes and failures will iron out some of these product characterization issues and uncertainties. But a more predictable and stable regulatory environment will depend, in part, on drugmakers publicly discussing their experiences taking cell therapies through the FDA.

"Cell therapy is still a relatively new field compared to other therapeutic modalities, and the industry hasn't yet coalesced on standard tools and strategies," Better said. "Having a larger database of product knowledge is always useful, even if there are some gaps." PMQ

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