PINK SHEET
CITELINE REGULATORY

23 May 2022 | **Analysis**

US FDA To Explore New Regulatory Pathways For Some Cellular Products

by Sue Sutter

Agency re-evaluating criteria for certain human cells, tissues and cellular and tissue-based products (HCT/Ps) that are not ideally regulated as BLAs; industry suggests a 2014 guidance which created an alternative pathway for cord blood products could serve as potential template.

The US Food and Drug Administration is considering whether new regulatory pathways are needed for certain types of human cells, tissues, and cellular and tissue-based products (HCT/Ps).

What types of HCT/Ps might fall into this new category, and what any new regulatory pathway might look like, remains to be seen. However, the agency's public announcement that it is willing to explore alternative pathways suggests a recognition that funneling certain types of HCT/Ps through the investigational new drug and biologics license application processes has not proved workable in practice, experts said.

> ***"We're aware that there are certain cell therapy products that do not fall clearly into our tissue rules as not requiring premarket authorization, and yet also are probably not regulated ideally by submission of full biologic biologics license applications." –FDA's Peter Marks***

During a recent Alliance for a Stronger FDA webinar on fiscal year 2023 budget priorities, Center for Biologics Evaluation and Research director Peter Marks briefly mentioned plans to explore alternative regulatory routes for some products in the HCT/P category.

PINK SHEET
CITELINE REGULATORY

The FDA will "probably start to explore what would be potentially intermediate pathways for certain cellular therapy products," Marks said. "We're aware that there are certain cell therapy products that do not fall clearly into our tissue rules as not requiring premarket authorization, and yet also are probably not regulated ideally by submission of full biologics license applications."

"We're going to explore whether there is some intermediate pathway that might be appropriate there. ... We are trying to lean in to those things that we regulate to find the best methods to bring them forward to the benefit of patients. Whether we'll find a solution there I can't say, but I think it's worth exploring."

Four Criteria

HCT/Ps are regulated solely under Section 361 of the Public Health Service Act, and do not require premarket review and approval, if they satisfy four criteria:

- Not more than minimally manipulated;
- Intended for homologous use only;
- Not combined with another article; and
- Either the HCT/P does not have a systemic effect and is not dependent on the metabolic activity of living cells for its primary function, or if it does the product is for autologous use, for use in a first- or second-degree blood relative, or for reproductive use.

Products that do not meet all of these criteria are regulated under Section 351 of the PHS, or under the Food, Drug and Cosmetic Act, as drugs, biologics or devices requiring FDA review and approval before commercial marketing, the agency said.

In November 2017, the agency announced its regenerative medicine policy framework and said it would exercise enforcement discretion for 36 months for certain HCT/P products with respect to IND and premarket approval requirements to give manufacturers time to come into compliance. This enforcement discretion applied to HCT/Ps that did not raise potential significant safety concerns. (Also see "*CBER Director Marks: Regenerative Medicine Enforcement Will Be 'Notched Up' In 2018*" - Pink Sheet, 17 Jan, 2018.)

Click here to explore this interactive content online

The FDA subsequently extended the enforcement discretion period by another six months in the midst of the COVID-19 pandemic. That period of enforcement discretion ended in May 2021, at

which point sponsors of Section 351 products without an IND or who were marketing without BLA approval risked agency action. (Also see "*Unapproved Cell/Tissue Product Enforcement Discretion Ends; How Hard Will US FDA Crack Down?*" - Pink Sheet, 28 May, 2021.)

Despite their efforts to encourage companies to come in and talk to the agency about the IND/BLA route, FDA officials publicly have lamented the continued broad marketing of unapproved products, particularly by stem cell clinics. During the enforcement discretion period, the FDA issued approximately 400 so-called "it has come to our attention" letters alerting sponsors of its compliance policy, as well as more than a dozen warning letters.

The agency also has filed lawsuits in Florida and California seeking injunctions against two stem cell clinics. (Also see "*US FDA Action On Regenerative Medicine May Be Hindered If Court Sides With Stem Cell Clinics*" - Pink Sheet, 1 Jun, 2021.)

Re-evaluation Based On Risk-Benefit Assessment

In response to questions from the *Pink Sheet* about Marks' comments on the Alliance webinar, the FDA said it currently takes a risk-based approach to regulation of HCT/Ps and "as such, we are re-evaluating the regulatory criteria for certain HCT/Ps based on a risk-benefit assessment."

Marks' comments "were intended to underscore our continued commitment to work with those who share our goal of advancing the development of safe and effective regenerative medicine products, including stem cell and related products, to benefit individuals in need," the agency said.

"Specifically, there are some products involving human cells and tissues (not necessarily stem cell products), which may not be optimally regulated using the current regulatory framework. Dr. Marks expressed his commitment to exploring if there might be a suitable alternative regulatory framework for such products."

The agency did not provide more detail as to the specific types of HCT/Ps that might be subject to a new regulatory pathway.

"FDA supports the safe clinical development of these products, and we are committed to continuing to work collaboratively with industry and the medical and scientific communities to provide the information and guidance needed to help foster the advancement of these promising therapies," the agency said. "We are focused on providing a clear pathway for those developing new therapies in regenerative medicine, while making sure that FDA meets its obligation to help ensure the safety and efficacy of the medical products that patients rely upon."

Why A New Approach May Be Needed

Several industry and legal experts suggested the agency's apparent willingness to explore an

intermediate pathway for some HCT/Ps is an implicit acknowledgement that the current regulatory approach for such a broad category of products is not ideal.

HCT/Ps often are customized products with customized manufacturing and assays, said Neil DiSpirito, a partner at Brown Rudnick in Washington, DC. "It really does not lend itself to one structured set of rules."

Creating additional pathways could help bring more product manufacturers into compliance, DiSpirito said. "If you only have one pathway and it doesn't fit everyone, then you're going to have a lot of people on the outside." However, if there are multiple pathways that capture 98% of HCT/Ps, "then there's really no excuse for people to be outside the pathways."

"I think what this is about is adjusting to newer products and newer circumstances," he said. "We always kind of say that oftentimes the law doesn't keep up with the technology. In this case, I think they're trying to keep the regulation more current with the technology."

Experts said many marketers of HCT/Ps are smaller companies and clinics that lack the resources needed to do large studies and embark on the formal approval process.

Mark Schwartz, a director at Hyman, Phelps and McNamara in Washington, DC and former deputy office director in CBER's Office of Compliance and Biologics Quality, said there was an expectation, set by the FDA, that the agency would try to lessen the regulatory burden for HCT/P manufacturers of lower risk products that did not meet the four criteria if they pursued the IND/BLA route.

In an April 2019 statement, Marks and then-commissioner Scott Gottlieb said that as the FDA approached the end of enforcement discretion, "we may take additional steps to delineate an efficient development path for promising products that pose lower risk to patients and that are being developed by sponsors who've engaged the regulatory process in a responsible manner by filing INDs. These would be cases where the sponsors have undertaken or are in the process of undertaking well-designed investigational studies with the intent of collecting information to more clearly identify the safety and benefits of their products."

"These companies have looked for guidance from FDA and have found it lacking," Schwartz said. "They were told that these companies would be given consideration, and it was unclear what was meant by that. But there was a suggestion that the regulatory requirements would not be so onerous as to make it unpalatable or impossible for small- or medium-size companies of lower risk products to do the clinical studies that would be necessary" before the product could be reintroduced following FDA approval.

However, for many companies of which Schwartz is aware, that has not been the case, he said.

PINK SHEET
CITELINE REGULATORY

Product Categories

The lack of detail provided by the FDA has left experts speculating as to what types of HCT/Ps might be included in an intermediate pathway and what that regulatory route might look like.

An intermediate pathway potentially could be opened for products that fail to meet one of the four criteria for regulation under Section 361, Schwartz said, where a risk assessment determines that the risks to a patient are minimal, adding that some believe the FDA's interpretation of the regulatory definition of "minimal manipulation" to be overly expansive. "Even if one of the four criteria is not met, does that always necessitate going all the way to a BLA for a product with viable cells, which is a huge jump?"

Subsets of products that could be ripe for an intermediate pathway include autologous cell therapies that are not cultured, tissues that have more of a device-like role in the body, or products used for treating orthopedic conditions, such as knee osteoarthritis and tennis elbow, experts said.

Some industry observers said the agency may be trying to draw a clearer distinction between stem cell clinics that make unfounded, and potentially unsafe, therapeutic benefit claims, and specialists' use of other types of HCT/P products that may be considered standard of care.

Kalah Auchincloss, executive VP-regulatory compliance and deputy general counsel at Greenleaf Health, noted the expansive growth in the stem cell clinic market in recent years. "That's probably an area where they are least likely to be flexible because there could be pretty serious consequences if stem cells go wrong," she said.

The FDA recognizes "the volume of products that could potentially be out there and the workload for industry and FDA, and they're trying to prioritize based on risk how to regulate these effectively," she said.

Cord Blood Pathway As A Template

In terms of what an intermediate pathway might look like, Kate Cook, principal-regulatory policy at Greenleaf Health, said that efficacy data requirements potentially could be reduced, with the product still regulated under a BLA. Another possibility is that regulatory standards for manufacturing could be modified to better address product characteristics in this class, she said, adding that depending on the pathway, statutory changes may be needed.

However, the agency also could pursue an intermediate pathway through guidance.

Several experts pointed to a March 2014 guidance on BLAs for minimally manipulated, unrelated allogeneic placental/umbilical cord blood for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system. Under this guidance, manufacturers

PINK SHEET
CITELINE REGULATORY

submitting a BLA for HPC, Cord Blood may rely on data previously submitted to a public docket regarding product standards, and establishment and processing controls, to demonstrate efficacy.

For example, the guidance states the chemistry, manufacturing and controls section of a BLA for HPC, Cord Blood products should contain a description of the specific tests and expected results that will provide information regarding the safety, purity, potency and identity of the product. The guidance includes the description and characteristics of the cord blood and HPC, Cord Blood – such as tests performed and the results – used to obtain the clinical data submitted to the public docket.

> ***The 2014 cord blood guidance "is a potential template … but I think it's fraught with difficulty if they're only going to allow some some cellular therapies to go down this pathway of a diminished regulatory burden." - Hyman, Phelps and McNamara's Mark Schwartz***

"These clinical data demonstrate the safety, purity, and potency of HPC, Cord Blood," the guidance states. "You would be expected to obtain similar test results using the recommended or other appropriate tests in order to rely on these clinical data in support of your BLA."

This guidance takes an approach in between Section 361 regulation and a full BLA, experts said, suggesting it could serve as a potential model for an intermediate pathway for HCT/Ps.

Schwartz said there was little controversy surrounding the 2014 guidance, but that may not be the case for any efforts to ease the regulatory pathway for some, but not all, HCT/Ps.

All cellular products are most likely to be biologics, and reducing the regulatory burden for some, but not all, cellular products "seems ripe for unending litigation" by those entities that are not able to take advantage of the new pathway and would likely assert there is no scientific or regulatory justification for being treated differently, he said.

The 2014 cord blood guidance "is a potential template … but I think it's fraught with difficulty if they're only going to allow some some cellular therapies to go down this pathway of a diminished regulatory burden," Schwartz said.

DiSpirito said an intermediate pathway could involve testing fewer patients or provide flexibilities on endpoints or for smaller prevalence diseases. Reliance on data from expanded access programs and other real-world evidence also are a possibility, he said.

It seems likely that any intermediate pathway for HCT/P products is a long way off, especially if statutory change is needed.

FDA user fee legislation marked up by the House Energy and Commerce Committee on 18 May would require a public workshop "to discuss best practices on generating scientific data necessary to further facilitate the development" of certain HCT/Ps that are regulated as drugs and biologics, "namely, stem cell and other cellular therapies." The workshop must be convened within three years following enactment, the bill states.