FDA Warning Indicates Scrutiny Of Regenerative Health Cos.

By **Dominick DiSabatino and Cortney Inman** (June 6, 2024)

Dominick DiSabatino

Cortney Inman

On May 21, the Center for Biologics Evaluation and Research, or CBER, at the U.S. Food and Drug Administration published a warning letter issued to Akan Biosciences Inc. for unresolved inspection observations following a back-and-forth between the FDA and Akan.

The Form FDA-483 highlights a number of observations about 585 vials of an Akan product, but the warning letter spends considerable time beforehand covering reasons why Akan's product does not meet the requirements of Title 21 of the Code of Federal Regulations, Part 1271.10(a), which qualifies certain human cells, tissues, or cellular- or tissue-based products, or HCT/Ps, for exemptions from key FDCA requirements, including premarket review.

Akan's product is an adipose-derived stromal vascular fraction cellular product for allogenic use with the brand name Ayama.

This warning letter is a quintessential example of the FDA's enforcement priorities for these products, and highlights the ongoing scrutiny placed on HCT/P manufacturers. We will have some analysis and takeaways later — including possible reasons for why the FDA opted to issue a warning letter as opposed to an untitled letter — but first, let's go through the details of the letter and what the FDA highlighted.

HCT/P Regulation

Our prior blog posts have taken a detailed look at the use of HCT/Ps and the FDA's risk-based regulatory framework for the same,[1] but it is important to note that the FDA views this area as "a complex and rapidly evolving field."[2] In short, as a reminder, if an HCT/P meets all of the following criteria, then the manufacturer can avoid the time-consuming and costly premarket review and approval process:

- The HCT/P is minimally manipulated;

- The HCT/P is objectively marketed for intended uses in the recipient that are consistent with its normal function in the donor's body, i.e., homologous uses;

- The HCT/P is not combined with another article, with some limited exceptions; and

- The HCT/P either:

- Does not have a systemic effect and is not dependent on the metabolic activity of living cells for its primary function; or

- Does have a systemic effect or is dependent on the metabolic activity of living cells for its primary function, and is for:

    - Use in the same individual who was the source of the tissue or cells;

    - Use in an individual who is a first- or second-degree blood relative of the donor of the tissue or cells; or

    - Reproductive use.

The purpose of this test is to help the FDA in differentiating HCT/Ps that pose minimal public health risks from those higher-risk products that should be subject to clinical trials and premarketing review by the agency.

Accordingly, HCT/Ps that do not meet the above criteria — and do not fall into one of the enumerated exceptions under Part 1271.15 — are considered to be drugs, devices or biological products regulated under Section 351 of the PHS Act and the Federal Food, Drug and Cosmetic Act.[3]

Without a doubt, the two most frequently discussed and cited criteria are minimal manipulation and homologous use. In evaluating minimal manipulation, the FDA looks at the processing of the product and evaluates the extent of steps involved in transforming the HCT/P from donor specimen to finished product.

Over time, the agency has provided a number of examples of minimal or more-than-minimal manipulation;[4] however, the FDA has also explicitly left this area open for innovation, stating that "subsequent accumulation of clinical data and experience about a particular process" may change the agency's assessment.[5]

For homologous use, the FDA considers the manner in which the product is marketed. In particular, the focus here is whether the HCT/P's intended use is to "perform[] the same basic function or functions in the recipient as in the donor."[6] For this step, the FDA considers the manufacturer's objective intent, as determined by product labeling, advertising, expressions of the manufacturer's representatives and circumstances surrounding distribution.

Here, the FDA's conclusion on the inapplicability of Part 1271.10(a), focuses on these two

subsections. The FDA simply states, without explanation, that Akan's product fails the minimal manipulation prong of the regulation because processing "alters the original relevant characteristics of the adipose tissue related to its utility for reconstruction, repair, or replacement."

On the homologous use prong, the FDA provides more context. The FDA notes that the product's basic function of "cushioning and support for … skin and internal organs, storing energy in the form of lipids, and insulating the body" is not what Akan advertises on its website — "to repair, reconstruct and replace your skin tissue."

For these two reasons, the FDA found that Akan's product does not qualify for exemption under Part 1271.10, and therefore is regulated as a drug and biological product.

The FDA further noted that Akan did not possess a valid biologics license or investigational new drug application for its product. Interestingly, unlike past warning letters for unapproved nonexempt HCT/Ps, the FDA did not explicitly state that Akan's actions "violated the FD&C Act and the PHS Act."[7] Perhaps this was an oversight on the agency's part, but nonetheless stands out among past enforcement.

Form 483 Observations

In addition, the FDA's letter also cited significant violations of HCT/P donor screening and eligibility testing and good manufacturing practice, or GMP, requirements. Among other things, the FDA's inspection revealed that Akan utilized inadequate methods to test and screen donors for communicable diseases.

For example, the FDA stated that Akan's donor screening questionnaire form failed to "address certain risk factors for relevant communicable disease agents and diseases, including ... a donor's risk of having West Nile Virus (WNV), among other risk factors."

In so doing, the FDA provided an extensive list of examples of risk factors that should be included on such forms. With respect to GMPs, the FDA further cited Akan for "[f]ailure to establish written procedures for production and process control" and "[f]ailure to have an adequate system for monitoring environmental conditions in an aseptic processing area."

Takeaways

This warning letter serves as yet another a reminder to HCT/P manufacturers of the FDA's core enforcement priorities with respect to cell and tissue products. While the FDA has issued a number of guidances over the years to help demystify the elements of Part 1271, also referred to as the tissue rules, the primary goal has always remained the same: prevention of the introduction, transmission and spread of communicable disease.

In achieving this goal, the FDA's tissue rules focus on three main areas:

1. Preventing unwitting use of contaminated tissues with the potential for transmitting infectious diseases such as AIDS and hepatitis;

2. Preventing improper handling or processing that might contaminate or damage tissues; and

3. Ensuring that clinical safety and effectiveness is demonstrated for tissues that are highly

processed, are used for other than their normal function, are combined with nontissue components, or are used for metabolic purposes.[8]

Perhaps unsurprisingly, then, the FDA keys on each of these concepts in its letter to Akan. The opening discussion of minimal manipulation and homologous use serves to further the third point, and reveals the FDA's assessment that products like Akan's should be subject to greater oversight.

Then, in addressing Akan's inadequate donor screening and testing procedures, the FDA focuses on the first point and the prevention of unwitting use of potentially contaminated tissues. Lastly, the discussion of Akan's GMP deficiencies focuses on the second point — prevention of improper handling and processing.

Furthermore, this letter also provides some helpful context for the types of activities that will lead to a warning letter versus an untitled letter. In terms of HCT/P enforcement, the CBER has historically kept a close eye on HCT/Ps. Indeed, this year alone, the CBER has issued six letters to HCT/P manufacturers.

In reviewing recent letters issued by CBER, we see that the agency tends to issue warning letters where donor screening and testing or GMP deficiencies are revealed during an inspection. In contrast, untitled letters typically focus more on the characteristics of the product as described in publicly available marketing claims made on company websites and social media pages.

Adding to this, the FDA has also advised that warning letters may be warranted for HCT/Ps where there are violations that "meet the threshold for regulatory significance suggesting that systemic problems exist within one or more areas of the firm's operations."[9]

This could include "continuing pattern[s] of non-compliance, a failure to correct significant deficiencies noted during a previous inspection, or the deficiencies pose a serious threat to the public health, and voluntary action is either not appropriate or can not be readily accomplished."[10]

Aside from these examples, the "threshold for regulatory significance" is not clearly defined. However, based on past letters, unresolved issues with donor screening and testing and GMP deficiencies certainly appear to meet this threshold.

According to the FDA, Akan was provided an opportunity to respond to these observations. However, the FDA found this response to be insufficient. Among other things, although Akan initiated a voluntary product recall of its Ayama product, the FDA deemed that the product recall documentation report disavowed any specific safety concerns regarding the product and Akan failed to provide the FDA with details regarding the remaining product on hand.

Further, the FDA noted that Akan's "revised process validation report for Ayama lack[ed] significant documentation to assure that the product has the identity, strength, purity, and quality it purports or is represented to possess."

Accordingly, the agency's motivation for issuing a warning letter was likely due to (1) the types of issues identified, i.e., donor screening and testing and GMPs, and (2) a failure to rectify these issues in an adequate manner, thereby suggesting systemic problems within the firm's operations.

All in all, this letter highlights the continued importance of not only strict adherence to the

FDA's tissue rules, but also taking a step back and remembering the bigger picture for why the FDA has crafted and implemented these regulations.

Further, if presented with a Form 483, companies should carefully consider what corrective actions will adequately address and alleviate the agency's concerns.

The FDA's tissue rules were intended to carefully balance the interests of innovation in regenerative medicine and the prevention of transmission of communicable disease. However, the CBER has made clear that it is not afraid to take action where there are obvious signs of noncompliance. In light of this, manufacturers should be mindful of the FDA's goals when determining a commercialization and manufacturing strategy for their product.

Dominick DiSabatino is a partner and Cortney Inman is an associate at Sheppard Mullin Richter & Hampton LLP.

[1] FDA Cracking Down on Unapproved HCT/Ps with Fourth Untitled Letter of 2023; FDA Issues First Untitled Letter of the Year to HCT/P Manufacturer.

[2] U.S. Food & Drug Admin., Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use: Guidance for Industry and Food and Drug Administration Staff, at 23 (July 2020).

[3] 21 C.F.R. § 1271.20.

[4] See, e.g.¸66 Fed. Reg. at 5457; Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use Guidance, at 15.

[5] See 63 Fed. Reg. at 26748.

[6] 21 C.F.R. § 1271.3.

[7] See, e.g., Warning Letter to Signature Biologics LLC (Sept. 18, 2023); Warning Letter to Row1 Inc. dba Regenative Labs (June 21, 2023); Warning Letter to Stratus Biosystems LLC dba CellGenuity Regenerative Science (June 5, 2023); Warning Letter to RenatiLabs Inc. (June 1, 2023).

[8] See U.S. Food & Drug Admin., Proposed Approach to Regulation of Cellular and Tissue-Based Products, at 6 (Feb. 1997).

[9] See U.S. Food & Drug Admin.,Compliance Program Guidance Manual: Inspection of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) 7341.002, at 17.

[10] See id.at 16, 18.