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FDA Convenes Two-Day Public Hearing on Human Cell and Tissue Product Regulatory Paradigm

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As stakeholders and watchers of the expansive field of regenerative medicine likely are aware, earlier this year a study published in the peer-reviewed journal *Cell Stem Cell* reported on the growth of so-called stem cell clinics operating in the U.S. It also examined the types of claims being made and treatments being marked by such businesses (we say so-called because some scientists dispute whether cells being used in these venues are "true" stem cells). Reports in the lay media of patients being healed or, conversely, injured by treatments administered in such clinics have also increased in frequency and detail over the past two years. Suffice it to say, therefore, that various applications and approaches that would fall under the rubric of "regenerative medicine" are receiving higher attention from the general public as well as greater scrutiny from scientists.

It is against this dynamic backdrop that the U.S. Food and Drug Administration (FDA or the agency) held a two-day public hearing on September 12 and 13, 2016 to obtain input on four recently issued draft guidance documents related to the regulation of human cells, tissues, or cellular or tissue-based products (HCT/Ps). It is uncommon for the FDA to convene a public hearing in order to receive feedback on proposed draft guidances – as opposed to proposed binding regulations or a broader public health initiative – and consequently, this action may indicate that the agency is planning to initiate widespread enforcement to exercise its HCT/P authorities more consistently across the United States.

Background

HCT/Ps intended for implantation, transplantation, infusion, or transfer into a human recipient have been subject to a distinct set of FDA regulations under the Public Health Service Act (PHSA) and the agency's authorities to prevent communicable disease transmission for several years. Lower-risk HCT/Ps are regulated solely under Section 361 of the PHSA, and these so-called "361 HCT/Ps" do not require any sort of pre-market approval by FDA before they can be marketed – meaning advertised, sold, and distributed – in the United States. Nonetheless, certain regulatory requirements do apply to facilities producing 361 HCT/Ps (such as annual registration with FDA, product listing, and compliance with applicable "current Good Tissue Practices").

In order for a cell or tissue-based product to be regulated solely under PHSA Section 361, it must meet all of the following criteria (set forth in the HCT/P regulations at 21 CFR 1271.10):

1. The HCT/P is minimally manipulated.
2. The HCT/P is intended for homologous use only (as reflected by labeling, advertising, or other indications of the manufacturer's objective intent).
3. The manufacturing of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent (as long as such agent does not raise new clinical safety concerns for the HCT/P).
4. Either:
    a. The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or
    b. The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells or its primary function, and it:
        i. Is for autologous use;
        ii. Is for allogenic use in a first- or second-degree blood relative; or
        iii. Is for reproductive use.

Any HCT/P that does not meet the required criteria for regulation solely as a 361 HCT/P is called a "351 HCT/P" – and in addition to the PHSA, it will be regulated under the Federal Food, Drug, and Cosmetic Act (FFDCA) as a drug, device, or biological product, depending upon its primary mode of action. Unlike the PHSA whose focus is on communicable disease transmission, the primary purpose of the FFDCA is to ensure the safety and effectiveness of regulated products that are introduced into commerce and sold to the American public. Safety and effectiveness of FDA-regulated prescription products typically are

demonstrated through large, controlled clinical trials that require significant financial resources, substantial human capital, and many years to complete. The relevant HCT/P regulations finalized by FDA in the early 2000's also incorporates a list of exceptions where none of these "361" or "351" regulations would apply, such as when a practitioner removes cells and implants them into the same patient "during the same surgical procedure."

This week's high-profile FDA hearing sought to receive broad stakeholder input on four draft guidance documents that further explain the agency's views on some of the criteria for a 361 HCT/P vs. a more highly regulated 351 product. Two of the draft guidances at issue describe what practices constitute "homologous use" and "minimal manipulation," and a third describes the scope of the "same surgical procedure" exception under 21 CFR 1271.15. The fourth and final document focuses on adipose (fat) tissue and cells obtained from adipose, which are being used clinically in many different patient populations without having been subjected to rigorous clinical studies or FDA premarket review.

Overview of FDA's Public Hearing

As mentioned above, the public hearing took place over two days at the main campus of the National Institutes of Health in Bethesda, MD, with approximately 150 people in attendance. In addition, the hearing was webcast live and the data for this now-archived webcast indicates that over 500 viewers watched at least some part of the event while it was taking place. These numbers reflect the widespread interest in FDA's policymaking with respect to cellular therapies, as well as the widespread impact such agency policies could have to various medical fields as diverse as neurology (many patients suffering with multiple sclerosis presented their views to FDA), oncology, orthopedics, wound care, and chronic pain.

Although many of the speakers who presented to the panel of FDA officials represented patients who rely on currently available cellular therapies or the commercial clinics in which those cellular treatments are being offered, the agency also heard views from academic researchers working in the stem cell field; from numerous diverse professional organizations both domestic and international; and from life sciences companies developing cell or tissue-based products that are intended to be marketed as prescription drugs or medical devices under PHSA Section 351. Some presenters advocated for the creation of an "in-between" regulatory pathway, to complement what they perceive as the "nothing" option for 361 HCT/Ps and the "everything" pathway that a 351 HCT/P has to take to get to market.

A concern voiced by several speakers was that unproven and untested 361 products have been flooding the market, especially in certain treatment areas like wound care, and are thus competing with FDA-approved products that have substantial data to substantiate their safety and effectiveness. In the wound care field specifically, several practitioners with years of human tissue experience expressed their dismay that it was often difficult for them to determine what products were approved vs. unapproved because both 361 and 351 HCT/P products are being labeled and marketed with identical claims.

But notwithstanding skepticism from scientists, physicians, and surgeons – and notwithstanding the gap in quality data that the public has about the frequency of serious adverse events associated with such treatments – many patients with serious diseases told FDA that their quality of life was significantly better after the treatment they received, and their stories are hard to forget. In response to patient concerns that effective treatments will be removed from the market by FDA after the agency finalizes these guidance documents, several speakers suggested that FDA consider the possibility of creating a high quality, mandatory, and publicly available patient registry to track everyone being treated using an unapproved HCT/P product. The proposed HCT/P registry would collect patient outcomes related to both efficacy and safety.

Certainly, the issues that will define how the HCT/P field progresses in the United States are myriad, complex, and fraught with political and medical sensitivities – even about whether "the government should regulate cells taken from my own body" (regardless of their further manufacture or manipulation) – and accordingly, this summary cannot capture every issue. However, nearly every speaker agreed that FDA needs to provide more regulatory clarity when it revises the four HCT/P draft guidances; provide more specificity by including examples to explain distinctions between two similar products that may be regulated under different authorities; and provide more consistency in its oversight of HCT/Ps as a whole. So on at least this one point, all stakeholders seem to be seeing eye-to-eye.

Regulatory and Legislative Outlook

Written comments to FDA in response to its public hearing notice must be submitted by September 27. Given the large amount of both scientific and anecdotal information the agency is expected to receive, which it will need to review and consider, finalization of the four draft documents is unlikely to take place before the end of the year. And although the FDA officials working on these complex issues are career employees with medical and scientific backgrounds – not political appointees – some delay in the release of final policies nonetheless can be anticipated due to changes in the White House and its Executive Administration in January 2016. As a result, it may be several months or even up to a year before FDA expands upon or revises these draft guidances and issues them in final form. A complete withdrawal of any of the drafts is unlikely.

At the same time, however, the REGROW Act (**S. 2689**) – first introduced in March 2016 by Senators Mark Kirk (R-IL), Joe Manchin (D-W.V.) and Susan Collins (R-ME) – could alter the way FDA implements or enforces the policies contained within the draft guidance documents (or in future final guidance documents). If enacted into law, this bipartisan legislation would seek to accelerate and create flexibility

in the premarket process for new regenerative medicine treatments. Under the language of the original REGROW Act, companies would be able to obtain conditional approval for a therapeutic product based on preliminary clinical evidence of safety and a reasonable expectation of effectiveness. The company would then be required to submit to FDA a full marketing application demonstrating product effectiveness after five years, or else risk the withdrawal of the treatment from the market. A revised version of the bill (circulated to stakeholders over the summer but not introduced formally, such that it is not available on Congress.gov), omits the 5-year conditional approval pathway in response to concerns about patient safety and provides instead for accelerated agency review and approval.

Senator Kirk has recently advocated for attaching the REGROW Act to the biomedical innovation package contained in the 21st Century Cures Act (H.R. 6), which was passed by the House in July of 2015. Although the 21st Century Cures Act is not currently slated for floor consideration in the Senate, Senate leadership has expressed support for considering the legislation before the end of the year. If the REGROW Act is not passed this year, supporters are hoping to attach the language to must-pass legislation codifying FDA-industry user fee agreements, because those user fee authorizations are up for renewal in late 2017.

Mintz Levin's Health and FDA lawyers, as well as the health policy experts at ML Strategies, are closely monitoring these HCT/P regulatory and legislative activities. Please contact any of us for more information or to discuss potential impacts on your business.

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