KING & SPALDING
Client Alert

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For more information, contact:

Eva Temkin
+1 202 626 5418
etemkin@kslaw.com

Elaine Tseng
+1 415 318 1240
etseng@kslaw.com

Christina Markus
+1 202 626 2926
cmarkus@kslaw.com

Jonathan Trinh
+1 202 626 8994
jtrinh@kslaw.com

King & Spalding

Washington, D.C.
1700 Pennsylvania Avenue, NW
Washington, D.C. 20006-4707
Tel: +1 202 737 0500

The End of Enforcement Discretion for Cell & Gene Therapies: *Thinking Through Next Steps*

Beginning this week, the U.S. Food and Drug Administration ("FDA") ended its compliance and enforcement discretion policy with regard to certain human cell, tissue, and cellular and tissue-based products ("HCT/Ps"). HCT/P manufacturers without an FDA-approved marketing application may find themselves subject to FDA scrutiny under the Federal Food, Drug, and Cosmetic Act ("FD&C Act") and the Public Health Service Act ("PHS Act"). Firms will have to think hard about whether to submit investigational new drug applications ("INDs") or marketing applications, wind down production, or risk running afoul of applicable laws and regulations governing unapproved biological products. They should also be mindful of how data collected to date can help to inform next steps.

I. Regulation of HCT/Ps

HCT/Ps are articles containing or constituting human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient.[1] They are regulated under sections 351 and 361 of the PHS Act and/or the FD&C Act and implementing regulations.[2] Generally, HCT/Ps will have undergone substantial manufacturing, and clinical data will be necessary in order to establish the safety and effectiveness of these products prior to marketing.[3] However, there are two exceptions to this general rule. First, FDA will exempt HCT/Ps from the premarket review and approval processes and regulate them exclusively under section 361 if they:

(1) have undergone only minimal manufacturing;

(2) are intended for homologous use;

(3) are not combined with another article; and

(4) do not have a systemic effect and are not dependent on metabolic effect for their primary function (with some exceptions).[4]

Second, FDA has explained that it views "autologous cells or tissues that are removed from an individual and implanted into the same individual without intervening processing steps beyond rinsing, cleansing, sizing, or shaping" to raise "no additional risks of contamination and communicable disease transmission beyond that typically associated with surgery."[5] As such, premarket review and other regulatory requirements will not apply to an HCT/P that is removed and reimplanted in its original form in the same individual during the same surgical procedure.[6]

II. Compliance and Enforcement Discretion Policy History

In the fall of 2017, FDA announced a temporary compliance and enforcement discretion policy, under which FDA applied a risk-based approach to enforcement actions for HCT/P manufacturers whose products were subject to the premarket review process but did not yet meet regulatory requirements.[7]

The enforcement discretion did not mean that FDA was turning a completely blind eye to HCT/P manufacturers that were marketing unapproved products. Indeed, the Agency stated its intent to take enforcement action against products that had safety concerns reported or that FDA believed had the potential to raise safety concerns. Thus, notwithstanding the enforcement discretion policy, FDA focused its enforcement actions on HCT/Ps that posed a higher risk, as measured by the products' route of administration and the diseases and conditions for which they were being used,[8] and issued at least 14 warning letters and 24 untitled letters to HCT/P manufacturers during the enforcement discretion period.[9] And, in a potential preview of things to come, FDA also sent approximately 400 "it has come to our attention" letters to various health care providers, clinics, and manufacturers of cellular products, alerting them that they may be marketing unapproved HCT/Ps and subject to FDA's compliance and enforcement policy.[10]

FDA initially intended the compliance and enforcement policy to last three years (through November 2020) to afford HCT/P manufacturers time to comply with the premarket approval requirements.[11] In July 2020, FDA extended the compliance and enforcement policy through May 31, 2021.[12] Leaders at the Agency, including Peter Marks, Director of the Center for Biologics Evaluation and Research ("CBER"), and Melissa Mendoza, Deputy Director for CBER's Office of Compliance and Biologics Quality, confirmed that the policy would not be extended beyond May 31, 2021.[13] The compliance and enforcement discretion policy is now over.

III. Implications for HCT/P Manufacturers

Beginning on June 1, 2021, manufacturers of cell and gene therapy HCT/Ps that do not hold an approved marketing application or fall within one of the two exempt categories described above, are operating at risk of violating the PHS Act and/or FD&C Act. Ultimately, such manufacturers need to engage with FDA, and in particular with CBER, to determine the path to an approved marketing application. In most cases, this means submitting a biologics license application ("BLA") under section 351(a) of the PHS Act. This type of BLA, known as a "stand-alone" BLA, will need to include (among other things) all of the data and information necessary to establish the ongoing quality, safety, purity, and potency of the HCT/P for its intended uses.[14] It will be particularly important for manufacturers of HCT/Ps to consider what data they may have collected through real world use of their products to date, including during the period of enforcement discretion, and how that data may be able to be used to support approval of their BLAs. The rapidly evolving chemistry, manufacturing, and controls ("CMC") standards and guidance for cell and gene therapy products should be consulted for important context.[15] An acceptable manufacturing facility inspection is typically required before a BLA can issue,[16] and many inspections have been significantly delayed during the current COVID-19 public health emergency.[17]

The first step toward compliance generally will be to open an IND to conduct clinical trials in support of such a BLA, and to engage in discussion with FDA regarding appropriate submission of a marketing application. In addition to standard BLA-focused meetings under the Prescription Drug User Fee Act ("PDUFA"), including initial pre-IND meetings,[18] CBER's Initial Targeted Engagement for Regulatory Advice on CBER Products ("INTERACT") meeting process allows for informal preliminary advice before the pre-IND phase.[19]

HCT/Ps also may qualify for designation as regenerative medicine advanced therapies ("RMAT"). This designation, which must be granted by FDA, can be requested either concurrently with an IND submission or by amending an existing IND. Cell therapies, therapeutic tissue engineering products, human cell and tissue products, certain human gene therapies and xenogeneic cell products, and combination products that include such therapies or products—other than HCT/Ps that fall within an exception and are regulated solely under section 361 of the PHS Act—will be eligible for RMAT designation if they are intended for serious or life-threatening disease or conditions, and preliminary clinical evidence indicates the potential to address unmet medical needs.[20] RMAT-designated products will receive the benefits of fast track and breakthrough therapy designation, including early interactions with FDA that can be used to discuss potential surrogate or intermediate endpoints to support accelerated approval.[21] This can also mean fewer COVID-19-related inspection delays.[22] RMATs may also receive priority review if they are intended to treat serious conditions and, if approved, would provide a significant improvement in the safety or effectiveness of the treatment of the condition.[23] RMATs also may be appropriate for approval through the accelerated approval pathway, and there may be additional benefits in terms of fulfilling associated post-approval requirements.[24]

Importantly, though, even active discussions with FDA will not preclude enforcement action, including issuance of warning and untitled letters, and potentially injunctions,[25] civil monetary penalties,[26] and seizure.[27] FDA has made clear that, for products that do not fall within one of the exempt categories, the risk of enforcement can be averted only by obtaining approval of a marketing application.[28] In fact, last month, CBER Director Marks drew a red line: Such products should not be marketed without FDA approval.[29]

IV. Recommendations

Manufacturers of cell and gene therapy HCT/Ps without FDA approval can take discrete steps to mitigate the risk of regulatory enforcement. Specifically, manufacturers should carefully review the applicability of exemptions from premarket review requirements to their HCT/Ps and consider if their products or distribution processes can be restructured to align with the exemptions. Where appropriate, manufacturers should prioritize engaging with FDA and initiating concrete steps toward preparing marketing applications. They should also ensure that, in the meantime, their HCT/Ps are used only under an IND. Alternately, manufacturers may consider winding down operations, particularly if the likelihood of obtaining an approval or qualifying for an exemption proves infeasible. If manufacturers choose to continue existing operations without taking corrective action, they operate at risk of FDA enforcement.

King & Spalding LLP regularly counsels pharmaceutical and biologics manufacturers on drug development and the submission of drug, biological product, and other marketing applications to FDA. Please let us know if you have any questions regarding the end of FDA's compliance and enforcement discretion policy.

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[1] 21 C.F.R. § 1271.3(d).
[2] FDA, Guidance for Industry, Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use at 3–4 (July 2020), https://www.fda.gov/media/109176/download [hereinafter "HCT/P Guidance"]; *see also* 21 U.S.C. § 355(a); 42 U.S.C. § 262(a); 21 C.F.R. Part 1271.
[3] *See* 42 U.S.C. §§ 262(a) and 264; 21 C.F.R. § 601.2(a).
[4] *See* 21 C.F.R. § 1271.10(a); HCT/P Guidance, at 3.
[5] FDA, Guidance for Industry, Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception at 3 (Nov. 2017), https://www.fda.gov/media/89920/download.
[6] *See* 21 C.F.R. § 1271.15(b).
[7] *See* HCT/P Guidance, at 22 n.32.
[8] FDA, Press Release, FDA Announces Comprehensive Regenerative Medicine Policy Framework (Nov. 15, 2017), https://www.fda.gov/news-events/press-announcements/fda-announces-comprehensive-regenerative-medicine-policy-framework.
[9] Melissa Mendoza, Deputy Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research, Address at the Food and Drug Law Institute: Key Issues in Regenerative Medicine Regulation and Approval (May 18, 2021).
[10] *Id.*; *see also* Peter Marks, *Advancing the Development of Safe and Effective Regenerative Medicine Products*, U.S. Food & Drug Admin. (Apr. 21, 2021), https://www.fda.gov/news-events/fda-voices/advancing-development-safe-and-effective-regenerative-medicine-products.
[11] *See* 82 Fed. Reg. 54290, 54291–92 (Nov. 17, 2017); HCT/P Guidance at 22 n.32.
[12] *See* HCT/P Guidance at 1–2.
[13] *See* Peter Marks, Director, Center for Biologics Evaluation and Research, Address at the Food and Drug Law Institute: Center for Biologics Evaluation and Research (CBER) Session (May 20, 2021); *see also* Mendoza, *supra* note 9, Marks, *supra* note 10.
[14] *See* 42 U.S.C. § 262(a); *see also* 21 C.F.R. § 601.2(a); HCT/P Guidance at 3–4.
[15] *See* 85 Fed. Reg. 5447, 5447–48 (Jan. 30, 2020); FDA, Guidance for Industry, Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (Jan. 2020); *see al*so FDA, Cellular and Gene Therapy Guidances, https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances (last updated Jan. 5, 2021) (providing directory to other FDA cellular and gene therapy guidance documents).
[16] 42 U.S.C. § 262(c); 21 C.F.R. § 601.20(d).
[17] *See* FDA, Resiliency Roadmap for FDA Inspectional Oversight at 2 (May 2021), https://www.fda.gov/media/148197/download.
[18] *See* FDA, Draft Guidance for Industry, Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products at 3 (Dec. 2017), https://www.fda.gov/media/109951/download.
[19] *See* FDA, *INTERACT Meetings*, https://www.fda.gov/vaccines-blood-biologics/industry-biologics/interact-meetings (last updated July 9, 2020).
[20] 21 U.S.C. § 356(g).
[21] *Id.*; FDA, Guidance for Industry, Expedited Programs for Regenerative Medicine Therapies for Serious Conditions at 6 (Feb. 2019), https://www.fda.gov/media/120267/download [hereinafter "RMAT Expedited Programs Guidance"].
[22] *See* Resiliency Roadmap for FDA Inspectional Oversight, *supra* note 17, at 2 (RMAT-designated products are considered "mission-critical" for inspection prioritization).
[23] *See* RMAT Expedited Programs Guidance at 9.
[24] 21 U.S.C. § 356(g)(6)–(7); RMAT Expedited Programs Guidance at 9–11.
[25] *See* 21 U.S.C. §§ 332(a) and 331(a)–(b).

[26] *See id.* § 333(a).
[27] *See id.* § 334(a).
[28] *See* Mendoza, supra note 9 ("At this point, that's not good enough to avoid potential compliance or enforcement action. So please, please do not count on any enforcement discretion going forward.")
[29] *See* Marks, *supra* note 13.