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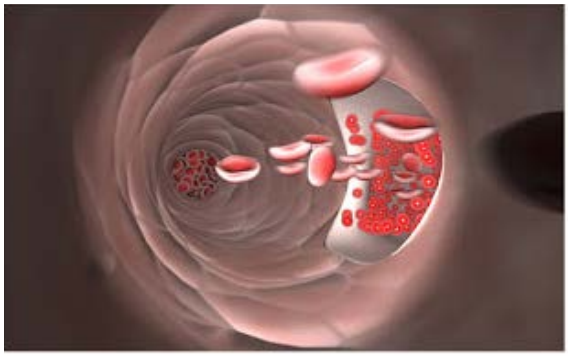
Proposed Legislation Would Create a New Conditional Approval Pathway to Market for Regenerative Medicine Products



Human cells, tissue or cellular and tissue-based products are known as HCT/Ps.

By Jeffrey K. Shapiro & Charlene Cho Hyman, Phelps & McNamara, P.C.

In the emerging world of regenerative medicine, there is a stark dichotomy in the level of regulation applied to products derived from human cells and tissues, or what FDA calls "human cells, tissue or cellular and tissue-based products" (HCT/Ps).

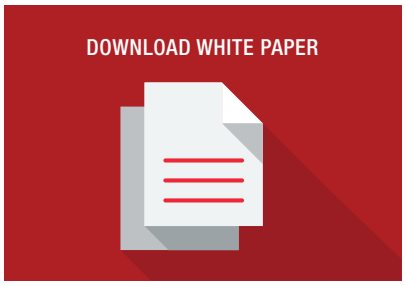
If an HCT/P meets certain requirements, it is eligible for regulation solely under section 361 of the Public Health Service (PHS) Act. A "361 HCT/P" does not undergo any premarket review by FDA prior to marketing. Once marketed, under 21 C.F.R. Part 1271, such products must comply with donor screening and eligibility requirements, as well as labeling, adverse event/manufacturing deviation reporting to FDA and product handling (Good Tissue Practice) requirements.

To qualify as a 361 HCT/P, a product must meet the following requirements in 21 CFR 1271.10(a):

- Be minimally manipulated;
- Be intended for homologous use (as reflected in labeling and advertising);
- Not be manufactured by combining cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent;
- Not have a systemic effect and not be dependent upon the metabolic activity of living cells for its primary function, with certain limited exceptions.

If any of these requirements are not met, the HCT/P is still subject to regulation under 21 C.F.R. Part 1271, but in addition is likely subject to biologic, drug or medical device regulation. In practice, many of the HCT/Ps in regenerative medicine that do not qualify as 361 HCT/Ps are regulated as biologics subject to section 351 of the PHS Act or "351 HCT/Ps." A 351 HCT/P requires approval of a biologics license application (BLA), typically supported by significant clinical data gathered under an Investigational New Drug (IND) exemption. The IND/BLA process is perhaps the most burdensome and lengthiest premarket review process that FDA imposes.

This regulatory framework has inhibited innovation by creating regulatory uncertainty in many cases as to whether a product is regulated as a 361 HCT/P or as a 351 HCT/P. The applicability of the 361 HCT/P requirements are often debatable, with said debate leading to one of two extremely different outcomes: no premarket review at all versus full IND/BLA review. Additionally, many products that arguably do deviate from the 361 HCT/P requirements simply do not pose a level of risk that would justify the high regulatory hurdles imposed in the IND/BLA process.



This article is related to the Q&A: Compliance with FDA' Good Tissue Practices.
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Congress is now considering a legislative solution, the "Reliable and Effective Growth for Regenerative Health Options that Improve Wellness" or the "REGROW Act." With rare bipartisan support in both the House and Senate, the REGROW Act was introduced on March 16, 2016 by Senators Mark Kirk (R-IL), Joe Manchin (D-WV) and Susan Collins (R-ME) in the Senate (S. 2689) and by Representatives Mike Coffman (R-CO), Mark Takai (D-HI) and H. Morgan Griffith (R-VA) in the House (H.R. 4762). The House Bill is identical to the Senate Bill, so for convenience, the discussion below refers only to S. 2689.

The REGROW Act would allow FDA to grant a five year conditional approval of a cellular or tissue therapeutic product that demonstrates preliminary clinical evidence of safety and a reasonable expectation of effectiveness. The firm is required to use this time to initiate an IND study and, ultimately, to submit a BLA for FDA to review.

There is no definition of what a "cellular or tissue therapeutic product" is, but it seems likely from the criteria that apply (described below) that this category corresponds to what FDA defines as HCT/Ps in 21 C.F.R. § 1271.10(a). (The bill refers to both "cellular" and "tissue" products, but some provisions and headings refer to "cellular" products while others refer to "cellular and tissue" products. And sometimes the word "therapeutic" is included and sometimes it is not. The inconsistencies appear to be unintentional.)

The conditional approval would cover the manufacture, distribution and sale as well as use of a cellular or tissue therapeutic product, provided that a BLA is filed within five years. Additionally, S. 2689 says FDA "may" continue the conditional approval during review of the BLA. (Given the length of BLA review, the bill should be revised to make it mandatory unless a significant safety concern exists.)

A number of requirements would apply in order for a product to qualify for conditional approval:

The manufacture, distribution and sale as well as use of the cellular or tissue therapeutic product must be consistent with the current regulations, including good manufacturing practices (GMPs).

The cellular or tissue therapeutic product also must satisfy all of the following criteria:

- The cells or tissue are adult human cells or tissues;
- The cells or tissues do not provoke a significant immunogenic response;
- The cells or tissues are either minimally manipulated and for a non-homologous use or more than minimally manipulated and for either a homologous or non-homologous use but in either case, not genetically modified;
- The cells or tissues are for a specific indication;
- The cells or tissues are produced exclusively for a use that performs, or helps achieve or restore, the same, or similar, function in the recipient as in the donor

(It may be worth noting that the language in the last bullet seems similar to the language defining "homologous use" in FDA's Draft Guidance on Homologous Use of HCT/Ps, which we blogged about here. Accordingly, the last bullet seems to contradict the third bullet, which allows the cells or tissue to qualify even if intended for a non-homologous use.)

During the five year conditional approval period, the sponsor must submit a BLA as well as annual reports and adverse event reports, which must contain all information generally required for approved biological products

The sponsor must have submitted an IND for treating the patients with the cellular therapeutic product during the five year conditional approval period.

And finally, the sponsor must not have obtained a conditional approval for the cellular therapeutic product for the same indication.

If all of the above-described conditions are satisfied, the cellular or tissue therapeutic product would be permitted to remain on the market unless and until FDA denies BLA approval.

The notion of applying conditional approval to these products is not as novel as it might seem. For many years, when an HCT/P has been found by FDA to have stepped outside the 361 requirements, the firm has been required to initiate an IND/BLA process, but has been in some cases also allowed to continue marketing under enforcement discretion if there is not a serious public health risk. In a sense, this statute would codify that approach but in a manner that provides greater regulatory certainty.

The last part of the bill addresses devices involved in the recovery, isolation, processing and delivery of cellular therapeutic products used in regenerative medicine. It includes language that does not alter the general regulatory scheme for devices, but seems intended to nudge FDA toward regulating with a lighter touch, focusing premarket review and classification of the devices based upon their functional performance in handling and preserving cells, as opposed to the specific clinical uses to which the cells are being put.

All in all, the REGROW Act deserves serious consideration. It holds out hope that the young regenerative medicine industry will be allowed to continue developing beneficial therapies in a way that is commercially viable, but with appropriate public health assurances. Whatever the shape of the final legislation, this draft is a good first step in the right direction.

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About the Authors

Jeffrey K. Shapiro *specializes in medical device law, advising and representing companies before FDA for more than 20 years. He has experience in FDA regulation of medical devices, including product clearances and approvals, MDR and Part 806 reporting requirements, labeling and advertising, recalls, and responding to Form 483s and warning letters. Mr. Shapiro also counsels clients on FDA requirements governing IVDs and HCT/Ps. Mr. Shapiro is an expert in FDA's regulation of combination products, including preparation of RFDs. As an advisor to start-ups, mid-sized, and large medical device manufacturers, Mr. Shapiro recognizes the operational and financial considerations involved in managing compliance and creating regulatory strategies.*

Charlene Cho*, Ph.D., advises clients about regulatory strategies, compliance matters, and the FDA approval process. With a doctorate in Neurobiology, Pharmacology & Physiology and over five years' experience working at FDA on regulatory policies and procedures, she is well positioned to provide technical advice and counseling on regulatory matters related to biologics, devices, and drugs.*

About MasterControl Inc.

MasterControl produces software solutions that enable regulated blood and biologics companies to get their products to market faster, mitigate risk, reduce overall costs and increase internal efficiency. MasterControl securely manages a company's critical information throughout the entire product lifecycle. Our software is known for being easy to implement, easy to validate and easy to use. MasterControl solutions include quality management, document management/document control, product lifecycle management, audit management, training management, bill of materials, supplier management, submissions management, and more. Supported by a comprehensive array of services based on industry best practices, MasterControl provides our customers with a complete information management solution across the entire enterprise. For more information about MasterControl, visit www.mastercontrol.com, or call: 800-825-9117 (U.S.); +44 (0) 1256 325 949 (Europe); or +81 (0) 3 6801 6147 (Japan).