Clearly Misunderstood Rules of the Stem Cell Road

THE OXYMORON OF HCT/P REGULATORY POLICY

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Introduction

For over three decades, medical advances and breakthroughs in regenerative therapies have paved the way for therapeutic use of human cells, tissues, and cellular and tissue-based products (HCT/Ps) in "implantation, transplantation, infusion, or transfer into a human recipient."[1,2] Specifically, embryonic stem cells (ESCs), induced pluripotent stem (iPS) cells, and adult stem cells (ASCs) can be harvested and potentially used to treat various diseases and conditions for which few therapies exist.[3] These stem cell therapies, e.g. autologous blood, bone marrow, and umbilical cord blood transplants, have become widely used and routinely offered as outpatient treatments.

At the same time, stem cell use has been plagued with controversy, since the first sheep, Dolly, was cloned in 1996 to more recent abortion politics and human cloning ethical concerns. Current contention revolves around the emergence of unlicensed, for-profit clinics that have illegally marketed these unapproved and unproven stem cell products directly to consumers and that have already collectively treated thousands of patients without federal regulatory approval.[4,5,6] 700 US clinics, clustered mostly in California, Florida, Texas, Colorado, Arizona, and New York, are known to be marketing unproven, unapproved, and unlicensed stem cell treatments or interventions to patients.[7] The news of these direct-to-consumer (DTC) clinics brings public health, safety, and regulatory concerns of HCT/Ps to center stage.

How can these stem cell clinics circumvent U.S. Food and Drug Administration (FDA) regulations? The likely reasons would point to misinterpretations of the current regulations and the existence of a legal loophole that allows HCT/Ps, meeting specific regulatory criteria, to be studied in clinical trials without prior FDA review and to be sold without formal premarket approval. The major issue here is that guidelines are ambiguous and insufficient, and the sponsor is often left to interpret the complex regulatory language in order to make a determination regarding whether their product is an HCT/P and if a FDA submission is required.[8]

The FDA is responsible for protecting public health by assuring safety, efficacy, and security of drugs and medical devices, as well as for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable.[9] With those tenets in mind, this policy paper will provide further proof of the inadequacies of the current HCT/P regulatory framework that has affected the accessibility of clinically effective stem cell therapies and has allowed what the FDA refers to as a "small number of unscrupulous actors who have seized the clinical promise of regenerative medicine" to market unapproved stem cell products directly to the public.[10]

Pre-Existing (Current) Federal Policies

In March 1997, the FDA released a document* "Proposed Approach to Regulation of Cellular and Tissue-Based Products" in the Agency's continuing effort to reduce unnecessary burdens for industry and to develop new therapies and products without diminishing public health protection from the risks of communicable disease transmission and from treatments that might be ineffective and potentially dangerous. From the subsequent public hearing to solicit information and views from interested parties concerning the proposed tiered, risk-based approach, the Agency designed a new, much needed comprehensive regulatory program for HCT/Ps set forth in 21 CFR Part 1271 and §361 of the Public Health Service Act†.[9,11] By 2005, the final HCT/P regulatory framework, composed of three final rules‡ and two interim final rules§, was established.[9]

In 21 CFR §1271.3(d), HCT/Ps are defined as "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. Examples of HCT/Ps include, but are not limited to, bone, ligament, skin, dura mater, heart valve, cornea, *hematopoietic stem/progenitor cells derived from peripheral and cord blood* [emphasis added], manipulated autologous chondrocytes, epithelial cells on a synthetic matrix, and semen or other reproductive tissue."[2]

HCT/P products are classified into three different regulatory categories based on risk to public health:[12,13]

1. Products not subject to HCT/P regulations, which are outside the scope of this paper.
2. HTC/P products that are minimally regulated and subject exclusively to the §361 tissue regulations of the PHSA are referred to as "361 HCT/Ps" only if they meet a set of five specific requirements in 21 CFR 1271.10(a), as summarized in the Table 1 below. These HCT/Ps, which includes stem cells, <u>do not</u> require premarket approval or FDA review prior to starting a clinical investigation.[8,9,12] The Agency notes that, if information does not exist to show that the minimal manipulation requirement is met, an HCT/P would then be considered a biologic or device, which suggests that the default opinion of the FDA is that prior Agency review is required.[8] FDA considers that if an HCT/P intended

* 62 FR 9721

† PHSA 42 U.S. Code § 264 - Regulations to control communicable diseases

‡ 66 FR 5447, January 19, 2001 "Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing" (registration final rule); 69 FR 29786, May 25, 2004 "Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products" (donor eligibility final rule), describes the requirements for donor screening and testing for "relevant communicable disease agents and diseases; 69 FR 68612, November 24, 2004 "Current Good Tissue Practice for Human Cell, Tissue, and Cellular and Tissue-Based Product Establishments, Inspection and Enforcement" (CGTP final rule), manufacturing to ensure HCT/Ps do not contain communicable agents; reporting; inspections

§ 69 FR 3823, January 27, 2004 "Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing" (interim final rule), addresses applicability; 70 FR 29949, May 25, 2005 "Human Cells, Tissues, and Cellular and Tissue-Based Products; Donor Screening and Testing, and Related Labeling" (interim final rule)

for use as an unproven treatment for a myriad of diseases or conditions, then the Agency will not consider it to be intended for homologous use only.[13]

3. HCT/P products that pose the most risk and that do not meet all criteria in 21 C.F.R. 1271.10(a), as per the FDA, are regulated either as medical devices under the Food Drug and Cosmetics Act (FDCA) and the PHSA 361[**] OR as a biological product under the FDCA and PHSA §351 and §361[††].[14,15] These HCT/Ps are also outside the scope of this paper.

Table 1. 361 HCT/Ps

361 HCT/Ps		
Requirement	**Regulatory Definition**	**Additional Guidance**
Minimal manipulation	"for structural tissue, processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement;" OR "for cells or nonstructural tissues, processing that does not alter the relevant biological characteristics of cells or tissues"[12]	December 2014 Draft Guidance "Minimal Manipulation of Human, Cells, Tissues, and Cellular and Tissue Based Products" distinguishing between structural tissue and cells or nonstructural tissue[12,16]
For homologous use	"repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor, including when such cells or tissues are for autologous use"[12]	October 2015, Draft Guidance "Homologous Use of Human Cells, Tissues, and Cellular and Tissue-Based Products" providing a broader insight into the Agency's thoughts on how to determine if an HCT/P is to be used or intended to be used for homologous purposes[13,17]
Manufactured or combined with no other agents	must not involve cells and tissues combined with other articles (subject to certain exceptions)	None
No systemic effects	must either not have a systemic effect "or depend on metabolic activity of living cells for its primary function," or, if it does have an effect or is dependent on the metabolic activities of cells, the product must be for "(a) autologous use, (b) [allogeneic] use in at most a second-degree blood relative, or (c) reproductive use"[12]	None
Registration	register and submit a list of every HCT/P manufactured within 5 days after beginning operations or within 30 days of the effective date of this regulation, whichever is later[12]	None

Regulatory Actions

The first federal action against a self-styled stem cell clinic was initiated against BioMark International Inc. in 2005. The owners were charged with wire fraud and drug marketing in connection

[**] 21 C.F.R. 820 and 1271 subparts A-D apply
[††] 21 C.F.R. 210, 211, and 1271 subparts A-D apply

with the selling of purported stem cell therapies for $10,000 to $35,000 per treatment (totaling at least $1.2 million) to patients suffering from ALS, multiple sclerosis, Parkinson's disease, and other incurable diseases.[18] FDA enforcement action shut down the company's business in the U.S., but the owners subsequently fled the country and resumed business using a new corporate identity in South Africa and the United Kingdom.[18,19]

The "misinterpretation" of the HTC/P regulations within 21 CFR 1271, with its complex definitions and classifications, is further evident in United States v. Regenerative Sciences. In 2008, the FDA sent an untitled letter to two physicians, Regenerative Sciences, and the Regenerative Sciences lab director, notifying them that their HCT/P, the Regenxx™ Procedure cell product (expanded autologous blood and bone marrow cells) constituted a "drug" under the FDCA and a "biologic" under the PHSA §351, thereby requiring premarketing approval prior to performing the Regenxx™ Procedure.[3] This triggered a long-drawn-out legal battle that centered on the question of whether processed autologous stem cells should be classified as a biologic drug, and therefore, federally regulated, or considered within the practice of medicine, which is not under federal jurisdiction.[3] The case was finally resolved in July 2012, with the court upholding the FDA's authority and issuing a permanent injunction against Regenerative Sciences.

Impact Analysis

Socioeconomics of Previous Regulatory Inaction on Stem Cell DTC Products

According to the world's largest-ever study of stem cell clinics, as published in *Cell Stem Cell*, advanced economy nations including Ireland, Singapore, Australia, Germany, Italy, Japan, and the U.S. (not developing economies) have the highest per capita number of clinics engaging in DTC marketing of putative stem cell therapies.[20] Significant revenues are generated from these treatments; and, from an economics standpoint, considerable profit incentive outweighs the perceived risks inherent in violating the law.[19] Will the "inconvenient" regulatory requirements encourage firms based in countries with strict oversight to shift their manufacturing and marketing into bordering towns and patients to seek treatments in foreign clinics that have little or no oversight?

"Stem cell tourism" was previously promoted in countries with weak laws or lax enforcement that enabled businesses to operate with relative impunity; however, this now includes developed countries like the U.S. Stem cell clinics seem to cluster in high concentrations near large metropolitan areas in states for reasons including: the relationship between number of clinics and population density; the regional variations in use of "alternative" medical interventions; aging population demographics; and the regulatory orientation of state medical boards and consumer protection agencies.[21]

Regulatory Loopholes In an Under-Regulated Industry

Stem cell clinics claim that they are complying with federal regulations and that they are engaged in the practice of medicine, which the FDA does not directly regulate, a position previously described in this paper and maintained by the American Society of Clinical Oncology (ASCO) in their outspoken assertions against the Agency's proposal of 21 CFR 1271 in the 1990's.[22,23,24] The clinics also maintain that their products are exceptions to 21 CFR 1271. Most notably, adipose-derived autologous stem cell treatments, which are not approved in the US marketplace, are being advertised and sold by clinics with these persuasive claims – evidence of a regulatory loophole.

The exception is found in 21 CFR 1271.15(b) and requires that three criteria are met:

- Establishments must remove and implant the HCT/Ps into the same individual from whom they were removed (autologous use);
- Establishments must implant HCT/Ps within the same surgical procedure;
- HCT/Ps must remain *such* HCT/Ps; they are in their original form

In summary, the exception explains "*you are not required to comply with the requirements of this part if you are an establishment that removes HCT/Ps from an individual and implants such HCT/Ps into the same individual during the same surgical procedure.*"[23]

In adipose-derived stem cell treatments, fat cells are removed from patients, stem cells are separated, and then re-injected into the same patient, mostly for cosmetic uses, e.g. "stem cell facelifts" and "stem cell breast augmentation," and therapies for a variety of diseases and disorders[‡‡]. Thus, the clinics maintain that the treatments are exceptions as defined in the regulation. Additionally, these clinics stress the principle of patient choice, assert that adipose-derived stem cell interventions are already known to be safe and efficacious, and claim that the FDA's bureaucratic approach to regulating clinical research is impeding the innovation and rapid development of stem cell therapies.[23] Furthermore, the stem cell clinics argue that the FDA should not insist that a licensed physician treating an individual patient with autologous stem cells be required to conform to the same pre-marketing and manufacturing requirements that bind large-scale, commercial drug companies that produce products for mass distribution. Has regulatory inaction emboldened these stem cell clinics, entrepreneurial physicians, and other market participants?

Despite clinic claims of being in compliance, the FDA interprets that most clinics are in violation of 21 CFR 1271 because they remove cells from processed fat tissue and return them to the patient's body, thus the process does not fall within the same surgical procedure regulatory exception.[23] Even

[‡‡] e.g., amyotrophic lateral sclerosis, spinal cord injuries, Parkinson's disease, multiple sclerosis, Alzheimer's disease, and muscular dystrophy

though "rinsing, cleansing, or sizing" and "shaping" are acceptable actions as per the regulations, the manufacturing steps required for adipose-derived stem cells are therefore not considered minimal manipulation as defined in 21 CFR 1271(a) and would typically cause the HCT/P to no longer be "such HCT/P."

Also, there is a lack of peer-reviewed evidence that these treatments are safe or efficacious; in fact, businesses often do not make their clinical protocols public or peer-reviewed data, so little is known about exactly what types of cells these clinics administer to patients. Therefore, the Agency maintains both that physicians who market and administer adipose-derived autologous stem cell treatments while claiming that they are at liberty to engage in the practice of medicine without having to comply with 21 CFR 1271 are incorrect and that without premarket approval, the product is an adulterated and misbranded drug and biologic under the FDCA and the PHSA.

In order to provide clarity and predictability regarding the 361 HCT/P qualification which was previously "murky" and to addresses what actions clinicians can perform while remaining within the scope of the exception, the FDA published two guidance documents[§§] in November of 2017.[6] It would be unlikely that these Agency guidance documents alone would stop clinics from making marketing claims and performing procedures; however, they may be an indication of the FDA's efforts in providing more sufficient, effective, and unambiguous oversight of stem cell clinics.

The Future of DTC Stem Cell Products – Concerns of Patient Access and Innovation

Some argue that HCT/P regulations are too restrictive and impede both medical innovation and patient access. The REGROW Act is an example of the current push from some political quarters and even from some individual stem cell researchers for lowering safety and efficacy standards for adult stem cell-based interventions.[21] These proponents of deregulation argue that current federal regulations governing the advertising, processing, and administration of autologous stem cells are too onerous and have resulted in few approved stem cell therapies reaching the American marketplace as shown earlier in this paper.[25,26]

At the same time, others urge rigorous standards and enforcement, given significant risks to patients of physical harm or exploitation, as we see with the FDA "crack-down" on stem cell clinics marketing their unapproved products. What we do know is that the diverse nature of HCT/Ps requires clear, comprehensive regulatory oversight to ensure safety and effectiveness – and likely, not just a single set of regulatory requirements. FDA added some clarity to 1271 by providing general definitions and

[§§] "Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception" and the single, final guidance "Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue- Based Products: Minimal Manipulation and Homologous Use.

examples of "repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues." However, the language is unclear in other ways and invites questions about what is not explained. For example, the FDA did not elaborate on what circumstances surrounding the distribution, independent of specific communications by the marketing company, could render use to be non-homologous.[13] Current HCT/P framework is ill-suited and collaboration to address this will need to include physicians and surgeons already using stem cell treatments, as well as the patients who have already had or want treatment. The Agency needs to reach beyond its existing "expert advisory committees" and public comment sessions.

Regarding patient access, a July 2017 paper reported that 18 US companies had registered "patient-sponsored" or "pay-to-participate" stem cell studies on ClinicalTrials.gov. This means that the patients receiving the treatment actually paid for them, which required in more legitimate studies. Only seven of the studies disclosed upfront that patients had to pay to join the study, and none of them revealed that the costs ranged from $5,000 to $15,000 per treatment. Most IRBs are likely unaware of such clinical studies, and many are not directly involved in them. Also, these studies had not been subject to FDA oversight or screening by NIH officials, nor were they gold standard studies, i.e. not randomized or blinded, which could bias the results.[27,28]

For those that contend that this is a patient's right to access issue and that FDA regulation is an invasion of individual privacy and a denial or personal autonomy, listing "pay-to-participate" studies in the ClinicalTrials.gov database would potentially cause confusion in research participants, making it difficult for the average patient to distinguish between commercial medical treatments and clinical research evaluating interventions. Even if there are few or no effective therapies, and limited or no access to experimental treatments, a well-intentioned referral from a physician may unintentionally put a patient at risk if the referral is to an establishment that advertises and administers unproven trials.

Final Thoughts

According to an article published in the New England Journal of Medicine, the FDA explains that *"without a commitment to the principles of adequate evidence generation that have led to so much medical progress, we may never see stem-cell therapy reach its full potential."*[29] Because there is no reporting requirement when therapies are administered outside clinical investigations, the onus is on the FDA to show that there is really a sustained commitment to enforcement with greater action against individuals and firms that persist in the unapproved marketing of stem cell interventions. Otherwise, the current situation with DTC stem cell marketing will prevail.

Compelling evidence from adequate, well-controlled clinical studies is needed in order to determine whether autologous and allogeneic stem cell therapies are safe and effective for their intended

uses. Without such studies, physicians will not be able to confidently, safely, and successfully treat their patients and regulators will not be able ascertain whether the clinical benefits of such therapies outweigh any potential harms.

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