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Mary Ann Chirba

Boston College Law School, chirbama@bc.edu

Alice Noble

Boston College Law School, alice.noble@bc.edu

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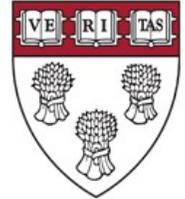
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Our Bodies, Our Cells: FDA Regulation of Autologous Adult Stem Cell Therapies

By [Mary Ann Chirba, J.D., D.Sc., M.P.H.](#) and [Alice A. Noble, J.D., M.P.H.](#)



Stem cells have been an endless source of fascination and controversy since Dolly the sheep was cloned in 1996. This month's announcement of a cloned human embryo from a single skin cell [1] came on the heels of Sir John B. Gurdon and Dr. Shinya

Yamanaka's receipt of the 2012 Nobel for Physiology and Medicine for their work with induced pluripotent stem cells. Pluripotent stem cells can be embryonic or induced. Embryonic stem cells (ESCs) can generally be obtained from human embryos or by cloning embryos through somatic cell nuclear transfer (SCNT), as was done for Dolly. Gurdon and Yamanaka demonstrated that pluripotent cells may also be formed by reprogramming adult cells to an embryonic state, resulting in *induced* pluripotent stem (iPS) cells without having to use eggs or cloning, or destroy embryos. However derived, pluripotent cells are capable of differentiating into virtually any cell type in the human body. This imbues them with great promise for scientific breakthroughs and medical advances, but also raises serious ethical, legal and safety concerns about their use.



Less controversial are “multipotent” adult stem cells (ASCs) which do not involve embryos or raise as many safety concerns as pluripotent cells. ASCs are found throughout the body. Their ability to differentiate is more limited than pluripotent cells but is vast nonetheless.

The NIH's clinicaltrials.gov site lists some 4500 ASC trials as compared with 27 for embryonic stem cells and 21 for induced pluripotent stem cells. Recent announcements of new stem cell treatments usually involve ASCs, such as last month's news that a toddler born without a trachea received a new one made from her own adult stem cells. It is therefore no surprise that ASCs have captured the attention of researchers, investors, physicians, patients and – increasingly – regulators, both here and abroad.

A growing number of physicians routinely offer treatments involving ASCs to their patients which can be performed in their offices. Autologous adult stem cells, used to treat a variety of conditions, are harvested from the patient, processed, and returned to the same patient. It is no surprise that moving ASCs

from laboratories to physician offices raises complex questions of law. We consider one of the more pressing ones: ***to what extent can the FDA regulate a physician's ability to treat a patient with that patient's own stem cells?*** In the coming months, the D.C. Circuit Court of Appeals will hear oral arguments on this very issue in *United States v. Regenerative Sciences*.[\[2\]](#)

The Regenerative Sciences case originated in Colorado where Christopher J. Centeno, M.D. and John R. Schultz, M.D. practicing jointly through the Centeno-Schultz Clinic (the Clinic), developed and used the "Regenxx™ Procedure" (the Procedure) to treat joint, muscle, bone and related conditions. Drs. Centeno and Schultz are majority shareholders in Regenerative Sciences (Regenerative) which owns the Procedure, licenses it exclusively to the Clinic, and provided laboratory services as part of the Clinic's use of the Procedure to treat patients. The Procedure involved taking blood and bone marrow samples from the patient at the Clinic; transporting them several miles to Regenerative where ASCs were isolated and cultured to "expand" or produce more cells; transporting them to the Colorado Genetics Laboratory for visual inspection to confirm the absence of genetic abnormalities; returning them to Regenerative; and some 4 to 6 weeks after initial extraction, transporting the resulting cell product to the Clinic for reinjection at the patient's site of injury or degeneration. Patients reported significant improvement while avoiding the physical and financial costs of invasive surgery. In 2008 the FDA notified the two physicians, Regenerative and Regenerative's lab director that the Regenxx™ Procedure cell product constituted a "drug" under the Food Drug and Cosmetics Act[\[3\]](#) and a "biologic" under the Public Health Service Act.[\[4\]](#) Consequently, the Procedure could not be used without first obtaining pre-marketing approval.

The FDA regulates medical drugs and devices under the FDCA and biologics under the PHSA, and requires some form of pre-

marketing approval for many of them. In doing so, however, it typically deals with commercial pharmaceutical companies; state law governs physicians in the practice of medicine. Thus, while FDA regulations obviously affect the drugs, devices and biologics available for physician use, they normally do not target a physician's actual treatment of a patient. Because medical advances routinely occur "at the bedside" without FDA oversight, the Regenerative defendants and the medical profession at large were deservedly surprised to learn that the FDA had decided to regulate autologous ASCs as human cell, tissue and tissue-based products (HCT/Ps).[\[5\]](#)

The FDA's HCT/P regulations can be found at 21 C.F.R. § 1271 and create a tiered framework based on PHSA §§ 351 and 361. We will not delve into its complexity here beyond saying that the agency predicates the extent of regulation on the degree of risk to a patient. PHSA § 361 provides minimal oversight of low-risk HCT/Ps that are, *inter alia*, 1) no more than minimally manipulated; 2) used for their same original or "homologous" purpose; and 3) autologous, i.e., the patient is treated with her own cells. PHSA § 361 manufacturers must comply with various registration and reporting requirements but do not need to obtain pre-marketing approval before using the HCT/P. In the FDA's view, even though the Regenexx™ Procedure is used for autologous (same patient) purposes, it involved more than minimal manipulation. This made the resulting cell product a "biologic" under PHSA §351 and a "drug" under the FDCA.

Consequently, Regenerative had unwittingly become an "establishment" that "manufactured" § 351 HCT/Ps. Treating a patient with her own cells had become "marketing" in need of prior approval by the FDA. Without pre-market approval, the cell product – based on the patient's own cells – had become an "adulterated" and "misbranded" drug and biologic under the FDCA and the PHSA. In effect, Regenerative would need to submit to the same pre-marketing approval process as Pfizer, the world's leading pharmaceutical company with self-reported revenues of \$59 billion for 2012. This was true even though Regenerative Sciences existed solely to enable its two

physician-owners to extract, expand and re-inject a patient's cells for the sole purpose of restoring that patient's function and reducing that patient's pain. Despite their dramatically different resources, Regenerative and Pfizer would be equally required to conform to Current Good Manufacturing Practices (CGMPs) and conduct formal clinical trials – quite the challenge when dealing with a patient who wants to use her own stem cells now as opposed to several if not many years in the future.

Litigation ensued and the case was eventually tried in the federal district court for the district of D.C. Regenerative challenged the FDA's authority to regulate at all, arguing: 1) Congress never intended its Commerce Clause power to interfere with the practice of medicine; and 2) there was no interstate commerce since all activities were confined to Colorado. The court disagreed, reasoning that state practice of medicine laws do not preclude federal law from affecting and effectively regulating certain aspects of a physician's practice. Further, interstate commerce existed because the Procedure used drugs shipped from out-of-state.

The court also upheld the FDA's ability to regulate a patient's own cells. Although "a close call," the court explained that the Regenexx™ cell product falls within the FDCA's technical definition of a "drug" because it is an "article ... intended to affect the structure or function of the body" [6] It simultaneously qualifies as a PHSA "biologic product" because like a "therapeutic serum, ... blood, blood component or derivative, protein ... or analogous product," it is "applicable to prevention, treatment or cure of a disease or condition in human beings." [7] Defendants' website and pleadings showed that the Regenexx™ Procedure and ASC treatment were "intended to affect the structure or function of the body" and "applicable to prevention, treatment or cure of a disease or condition in human beings." The FDA therefore had authority under both statutes to promulgate and enforce HCT/P regulations, and tie the degree of oversight to the degree of cell manipulation. The Procedure's "many steps" [8] could constitute more than manipulation under § 351 and, in any event, the agency's finding of more than minimal manipulation

deserved “substantial deference” by the court. Accordingly, the court entered summary judgment for the FDA, dismissed all counterclaims, and permanently enjoined use of the Regenexx™ Procedure. On appeal, each side has essentially stood firm in their positions, with Regenerative receiving the support of amici American Association of Orthopaedic Medicine, the Association of American Physicians & Surgeons, Inc. and Tim Turner (whose Parkinson’s disease has not responded to available treatments).

At first glance, the idea of the FDA regulating our own cells looks like an outrageous invasion of individual privacy and denial of personal autonomy. If patients weigh risks and benefits of medical treatments every day, why prevent them from doing so with their own cells? This question is especially compelling where a patient has few or no effective therapies, and limited or no access to experimental treatments. That a treatment may be more risky in the hands of untrained or unskilled doctors is not unique to autologous adult stem cell therapies; this problem pervades medical practice.

Despite the intuitive appeal of defendants’ position, a closer look at the medical procedures, the applicable statutes and the trial court’s assessment of both indicates that the FDA has the stronger argument on all counts. Using components shipped between states has frequently sufficed as interstate commerce in past case law. The cell product and its intended use do fall within the statute’s literal and technical definitions of a drug and a biologic as well as the regulatory definition of a human cell, tissue or tissue-based product.

If the agency’s power and discretion to regulate are upheld, the facts of this case are problematic because the degree of manipulation determines whether an HCT/P must satisfy the burdensome criteria of § 351 or § 361’s comparatively milder requirements. The Regenexx™ Procedure involves “many steps” to isolate and expand the cells including “selective culture and expansion of a multitude of different types of blood-forming and rare bone marrow stromal cells using plastic flasks, additives and nutrients, and environmental conditions

such as temperature and humidity, to determine the growth and biological characteristics of the resulting cell population.”[9] Over the course of 4 to 6 weeks, the cell product is moved between several locations: the Clinic, the Regenerative Sciences lab, an outside testing lab, back to Regenerative, and back to the Clinic.

These facts create a strong case for finding minimal manipulation. Plus, courts routinely defer to agency rule-making, interpretation and enforcement especially in matters of science and technology. Although the arguments for each side are more complex and nuanced, the big picture seems to show that the stars are in alignment for the FDA which, in our assessment, will likely prevail at the appellate level. ***This is not to say that we hope the government succeeds in derailing autologous adult stem cell therapies.*** We simply think the rules of statutory interpretation and administrative procedure will weigh in the agency’s favor in this case, especially with this particular set of facts.

Regardless of how the D.C. Circuit resolves this case, one thing is clear: the FDA should re-examine its HCT/P regulations especially as applied to physicians treating patients with their own cells. Extracting a patient’s cells for subsequent reinjection undoubtedly carries risk – but so does banking one’s own blood or freezing eggs for later use. Conditioning the extent of regulation on the degree of manipulation may make sense on paper but is vague and confusing in practice, especially in the dynamic field of cellular therapies. In an age of relentless cost inflation and limited therapies for debilitating illness, it makes no sense to deprive patients of autologous therapies because their physician lacks the resources – and patients lack the time – to satisfy the pre-marketing requirements that oppress even Merck and Johnson & Johnson. The FDA is obligated to protect the public health as well as individual patients. Critical to this mission is striking the proper balance of risks and benefits, where the benefits include facilitating medical innovation. In the context of adult stem cell regulation, especially autologous cells, it is time for that risk-benefit balance to be recalibrated. ***Stem cell therapies, even autologous ones, should be***

regulated, but those regulations must be re-designed to fit the parties and products being regulated. To be blunt, it makes no sense for the FDA to insist that a practicing physician who is treating an individual patient must conform to the same pre-marketing and manufacturing requirements that bind large-scale, commercial pharmaceutical manufacturers that produce drugs in bulk for mass distribution. Moreover, the agency should not monopolize risk-benefit calculations to the exclusion of patients who, with the counsel of their physicians, want to make their own calls about using their own cells to treat their own conditions. Preventing them from doing so is already leading many patients to assume other and perhaps greater forms of risk, such as seeking treatments in foreign clinics that may or may not be up to the task.

Suing an agency is usually an uphill and often losing battle. We doubt that Regenerative Sciences and cases of its kind will do much to lower regulatory hurdles. ***Some form of regulation is needed, but the FDA must recognize that its current HCT/P framework is ill-suited to many kinds of cellular therapies.*** It could revamp its HCT/P framework entirely, but that will take time. In the near term, the agency should reach beyond existing expert advisory committees and public comment sessions. It should engage in a true collaboration with a wider group of physicians and surgeons who are already using or stand ready to use various types of autologous adult stem cell therapies, and the patients who have had or want treatment. It can also look to the guidelines of relevant organizations, such as the American Association of Blood Banks or various physician organizations. Only then can the FDA get a firm handle on what kinds of techniques and treatments present tolerable levels of risk when balanced with the need for innovation and the basic right of patients to use their own cells. After all, patients are the ones who must bear the burdens of illness, not the regulators, judges or attorneys.

[Cross-posted from [HealthLawProf Blog](#)]



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Tassel, Pharmaceuticals, Stem Cells and tagged Bioethics, biotechnology, FDA, health law policy, HealthLawProf Blog, human tissue, pharmaceuticals, stem cells by Katharine Van Tassel. Bookmark the [permalink](#).

6 THOUGHTS ON "OUR BODIES, OUR CELLS: FDA REGULATION OF AUTOLOGOUS ADULT STEM CELL THERAPIES"



[James Vanden Bosch](#) on [June 5, 2013 at 11:52 AM](#) said:

Beautiful and insightful commentary! I, myself with medical doctors throughout the world, have been in the practice of autologous stem cell treatments for orthopedic, Dr. Joseph Purita, neurological and autoimmune conditions. I have seen many patients that have the financial burdens of too costly of medical treatments only to run out of options as conventional treatment are not working. I have performed in excess of over 6,000 treatments in the past 6 years to see patients overcome illness where conventional therapies have failed. Thank you.



[Geoffrey Lomax](#) on [June 6, 2013 at 1:27 PM](#) said:

A very comprehensive and informative review of the state of regulation of autologous cell therapies and some provocative thinking about the balance between safety and freedom of choice. I expect we will be struggling with this balance for the foreseeable future. Thank you!

Technical note, the authors state:

The NIH's [clinicaltrials.gov](#) site lists some 4500 ASC trials as compared with 27 for embryonic stem cells and 21 for induced pluripotent stem cells.

I attempted to replicate the embryonic stem cells search using different approaches (e.g. search term,

intervention and embryonic stem cells) with 26 resulting records. An examination of the resulting records reveals:

6 involve actual clinical interventions with hESC-based therapies for eye disease

The remaining records are not “trials” involving hESC-based interventions.

8 involve cell line differentiation, cell characterization or biomarker studies

8 involve interventions using drugs, cord blood or other adult cells

4 involve the derivation of cell lines

My current understanding is there are 6 hESC-based clinical trials in progress and 1 trial has been terminated. I mention this because the figure of 27 trials is misleading, and it has already been disseminated on social media.

Given the apparent 4-fold discrepancy between these figures, I would encourage additional explanation of the results or a revision of the reported number to best reflect the state of the field.

Respectfully.

Geoffrey Lomax
CIRM



[Paul Knoepfler](#) on [June 6, 2013 at 5:32 PM](#) said:

The historical and legal perspectives in the first half of the article are spot on and helpful.

However, parts of the later portion where you argue for

weakening of the regulation of propagated adult stem cell therapies greatly concern me and you have left out some very important elements that are key to understanding the ongoing debate over the appropriate level of regulatory oversight for stem cell therapies. For example, you pretty much gloss over the safety concerns related to these stem cell interventions.

It seems to me that changes are definitely needed at the FDA in some respects related to stem cells such as expanded compassionate use of stem cells for patients with fatal diseases and a push for more openness. So we agree on a need for change at the FDA on stem cells. But the weakening of regulatory standards for propagated adult stem cell interventions would greatly increase patient risk. Further, as the numerous outstanding adult stem cell biotechs such as Athersys and Mesoblast have shown, in the stem cell field a company can have its innovation and be compliant too.

Your statement, "Conditioning the extent of regulation on the degree of manipulation may make sense on paper but is vague and confusing in practice, especially in the dynamic field of cellular therapies" is very puzzling.

In fact, the degree of manipulation is operationally (not just on paper) extremely important from a patient safety perspective and it makes perfect common sense that stem cells manipulated in different ways and to different degrees should be subject to different regulations. I do not see what's vague or confusing about that at all.

On the other hand, your argument that smaller companies producing stem cell drugs should not be subject to the same regulations as larger companies is a dangerous one. Since when is the law variable depending on the size of the entity that should be following that law? Just as small and large drug manufacturers of pill (chemical) drugs have to follow the

same rules to provide data on safety and efficacy, smaller companies selling stem cell drug interventions should have to follow the same rules and laws as big companies. To do otherwise would put patients at great risk. Don't underestimate the number of patients collectively that stem cell clinics are treating and putting at risk these days: the numbers are in the many thousands and growing.

Paul Knoepfler

UC Davis

<http://www.ipscell.com>



Alexey on June 8, 2013 at 9:07 PM said:

As Goffrey pointed out, the authors completely off with numbers of clinical trials. This is very misleading for the public. Unlike the authors of this post, he spend some time to read it through the trials (it's easy thing to do for iPS and hES trials) and got the right numbers.

Everyone can do this correct data mining. Just take some time, before throw some numbers for public view.

As for iPS, out of 21 listed by authors in the post, 0 trials are therapeutic. Out of >4500 more than 70% are drugs and combinations for hematopoietic progenitor cell transplant for homologous use in hematology-oncology. All of these assess drugs for conditioning regimen or something else, but not efficacy of cells themselves.

Finally, NCT database represents about 75% of world's available clinical trials registries and therefore doesn't give the whole picture.

Unfortunately, the authors are not addressing comments above.



Alexey on [June 9, 2013 at 2:19 AM](#) said:

I think, everyone could agree, that FDA needs to reform and tune up a current view (regulations) on some (or many) kinds of cell therapy. I think, agency understands it, but can't modify the current law quickly, because of novel and uncertain nature of cell therapies.

As Geoffrey pointed out, there is a huge discrepancy between number of trials, indicated by authors and reality. Unlike the authors, he did a great analysis and came with a correct real picture. It is very important to read through trials and understand what is all about. Throwing numbers, retrieved by search results, without sorting it out and hand coding, could mislead public hugely.

As for iPS, out of 21 listed by authors in the post, 0 trials are therapeutic. Out of >4500 more than 70% are drugs and combinations for hematopoietic progenitor cell transplant for homologous use in hematology-oncology. All of these assess drugs for conditioning regimen or something else, but not efficacy of cells themselves.

Finally, NCT database represents about 75% of world's available clinical trials registries and therefore doesn't give the whole picture



Gabriel Rosenfeld on [June 11, 2013 at 3:22 PM](#) said:

I really enjoyed this article having some experience on the research side with embryonic stem cells. Perhaps this is too simplistic but would it be unreasonable to assert that patients suffering from degenerative or terminal diseases be exempt from regulations on use of their own cells from a humanitarian position? Well, not exempt per se. I think it would be useful to mandate reporting the specific therapy/patient progress to FDA to

monitor effectiveness perhaps within a specified period of time to allow the providers to patent their procedure. Nonetheless, I think that Paul raises an important point regarding safety if we simply allow small organizations looser regulations.

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