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Safety and Regulatory Issues Regarding Stem Cell Therapies: One Clinic's Perspective

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Abstract

Stem cells therapies have been in preclinical development for the past 2 decades. A rapidly evolving regulatory landscape has restrained many of these technologies from advancing from the bench to the bedside. Although the large-scale clinical safety of stem cell therapies remains to be fully tested, the total number of patients who have safely received these therapies is large and growing. Prima facie evidence would dictate that certain types of cell therapy are likely safer than others. Understanding the current regulation regarding stem cells involves a discussion of their safety profile, as the 2 issues are closely intertwined.

The Historical Regulatory Landscape

The United States Food and Drug Administration (FDA) has traditionally regulated chemical drugs. It began to regulate biologic products in terms of vaccines in 1913 with the Virus-Serum Toxin Act [1]. The Public Health Service Act (PHSA) was created in 1942 and included this regulation, as well as others, which later applied to the reduction of communicable disease in organ transplants [2]. Before the 1990s, cells were regulated only as devices or as transplant tissue [3]. In fact, the regulation of the cartilage repair product Carticel is a good example of the regulatory change initiated by the FDA in the 1990s regarding cells.

Carticel is a service whereby autologous cartilage cells are harvested from the donor, culture expanded to greater numbers in a distant laboratory, and then sent back to the surgeon for reimplantation under an osteochondral flap [4]. The service was first approved in 1995 under the Center for Devices and Radiological health (CDRH) section of the FDA, which approves new medical devices. Shortly thereafter, the Center for Biologics Evaluation and Research notified the purveyor of the service that Carticel should be regulated under its new Biologics License Application (BLA) process. Genzyme then submitted level V case series data, and the service was approved as a "biologic product" in 1996 [5]. Carticel is an apt demonstration of both the industry response to added regulation and the effects of this regulation on innovation.

In the late 1990s, the FDA publically proposed regulating more than minimally manipulated cells (MAS cells) as drugs [3]. This classification included any cells that were culture expanded (multiplying cell number in culture while retaining multipotency). Public hearings were held, at which many industry groups, professional groups, and academia voiced opposition. For example, the American Red Cross submitted written testimony that it opposed the position that cultured cells should be regulated the same as drugs, instead proposing that they be regulated more like medical devices [6]. The American Society of Clinical Oncology stated vehement opposition in their written testimony, "ASCO objects in the strongest terms to the FDA's proposed regulation of stem cell transplants. This misguided proposal is unnecessary, would jeopardize the proper treatment of cancer patients and impede the development of new therapies, would substantially increase the cost of stem cell transplants, and exceeds the FDA's legal authority" [7]. Northwestern University also opposed this new regulatory proposal, as did other groups such as the Society for Assisted Reproductive Technology, the Biotechnology Industry Organization (BIO), and biologics companies such as Reprogenesis and Osiris Therapeutics [8].

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The Landscape Changes

After the late 1990s, the FDA created regulations that allowed it to classify allogeneic cultured cells using the BLA drug pathway [9]. This meant that practically, as these products would require FDA approval using extensive clinical trials for each medical indication, that they would be treated like new drugs. To the extent that these cells were grown en masse and manufactured and widely distributed like chemical drugs, this made common sense. However, at about the same time, a new concept in therapy was being studied in the peer reviewed literature—autologous stem cells [10]. These plentiful cells could be extracted from the bone marrow for autologous use and in animal models showed promise to treat diabetes, arthritis, neurologic disorders such as stroke, and cardiac diseases such as myocardial infarction.

In 2006, the FDA changed its regulatory focus, dramatically broadening its regulatory authority, as noted by legal scholar Mary Anne Chirba [11]. Without prior notice for comment and rule making, the agency changed a single word in the newly developed 21 CFR 1271, cellular product regulations, from "another" to "a." The wording went from (into another human), focusing only on allogeneic transplants, to (into a human), thereby dramatically expanding the scope of the regulations to also include autologous therapies. As Chirba points out, this had the net effect of applying the regulations of what were previously described as surgical procedures, where tissue is transferred from 1 part of the body to another, to autologous cells. This change was likely only noted by the most ardent watchers of regulatory law, as the 1-word change appeared only in the new version of the Federal Register.

Safety in the Context of Regulation

Drugs are mass manufactured and distributed. One batch of tainted drugs or an unsafe drug could potentially injure millions of unsuspecting individuals. As a result, strong drug regulations are an important part of the regulatory safety net necessary to protect patients. Although surgical procedures can be similarly injurious per event, each patient is consented for the risks and benefits for that specific procedure, and makes a conscious decision to proceed or to forego the surgery. As a result, surgical procedures have been regulated under the practice of medicine, which in the United States is regulated by state medical boards [11].

The FDA's 2006 change to include autologous cells, as pointed out by Chirba, had the practical effect of extending drug regulations into the practice of medicine. This essentially provided double regulation (federal and state) over what had been traditionally regulated only by states. In addition, it created a host of issues for physicians caught in the regulatory safety net, as none can afford or meet the strict standards for drug approval and production.

What Does the Regulation Say?

According to 21 CFR 1271, not all autologous cells are drugs, although what is a drug and what is not is sometimes difficult to understand. First, the term used to describe cells in the regulations is HCT/P (denoting human cells, tissues, and cellular and tissue-based products). Second, a "line in the sand" approach has been used by the agency based on the level of intended use, source, and manipulation of the cells. In general, if an HCT/P is used for the same function as it serves in the body and is less processed, it is either classified as a less regulated 361 biologic tissue or is exempt from regulation when used by a physician [9].

An important aspect of the 1271 regulations is "more than minimal manipulation." The HCT/P falls into this category when they are more than minimally processed. The allowed processing steps include centrifugation, addition of crystalloids, water, cutting/shaping, and other procedures that are commonly used in whole-tissue processing. If nothing more than these steps are used, then the autologous cells are exempt from drug regulation. As an example of what is not "minimally manipulated" and therefore considered a drug, the FDA has recently stated in separate warning letters to both New York– and Pennsylvania-based plastic surgeons that the use of an ultrasonic technology to break down the structure of autologous fat to obtain fat stem cells creates a new drug [12,13]. Furthermore, if the HCT/Ps are minimally processed and for homologous use (ie, used for the same function that they serve in the body), they are considered "minimally manipulated" and thus exempt from drug regulations.

The reasoning behind what is determined to be homologous or not can be difficult to interpret. For example, the FDA Tissue Reference Group (TRG) informed a Maryland Plastic Surgeon in 2012 that stromal vascular fraction cells that were isolated from enzyme-digested adipose tissue and that were to be used for adipose breast reconstruction were not homologous use and therefore were a drug [14]. However, it is difficult to follow how this adipose-to–adipose subcutaneous transfer could be anything but homologous use.

Finally, yet another important aspect of the regulations for physicians is the same surgical procedure exemption [21 CFR 1271.15(b)]. The general concept is that autologous cells are exempt from drug regulations if the cells are processed during the same surgical procedure. However, recently the FDA has shown that it will interpret this portion of the regulation narrowly. For example, a recent request to the TRG from a Colorado practice is illustrative [15]. When asked if autologous adipose tissue processed via enzyme digestion to isolate the stromal vascular fraction (ie, stem cell component of fat) would be considered minimal manipulation, the FDA took issue with the process along many lines. Still, perhaps the most intriguing reason given why the HCT/P

would be regulated as a drug, despite being processed at the bedside during the same procedure, was that the process had "too many steps."

Our Experience

In 2005, our medical practice began the process of studying the use of both surgical procedure—isolated bone marrow stem cells (buffy coat) and culture-expanded mesenchymal stem cells. We first queried the FDA Center for Biologics Evaluation and Research (CBER) about our plans, but their response was unclear regarding what treatments would be regulated by the FDA. As a result, we proceeded to obtain multiple legal opinions that autologous culture expansion in our own patients was the practice of medicine. After a 2-year, self-funded, institutional review board—approved study in almost 50 patients, we chose to move forward with patient care after being impressed with the results in peripheral joint osteoarthritis and observing an excellent safety profile. From this clinical work, several imaging case studies were published [16,17].

In 2008, we received an untitled letter from the FDA CBER, stating that our autologous culture expansion could represent the creation of a drug without a biologics license in place [18]. We sent letters from counsel to the FDA, honestly believing that because counsel had already opined that the agency had no authority over a physician, the matter would be quickly handled. Instead, in 2009, the FDA inspected our medical practice using drug factory manufacturing standards. Shortly thereafter we filed for a restraining order in Denver district court, as the FDA's intervention was affecting our day-to-day medical practice operations. That case was dismissed by the Denver district court on grounds that the issue was not "ripe" for judicial review, as the FDA had not formally stated we were violating any regulations, and as an "untitled letter" had no legal significance. In 2010, after a second inspection, we filed for a restraining order in the DC District court, and the FDA responded with filing an injunction to stop our use of cultured MSCs in patients. We voluntarily stopped the use of this therapy pending the final outcome of the lawsuits. In 2012, Judge Collyer, of the U.S. District Court, sided with the FDA's position that culture expansion constituted the creation of a 351 biologic drug. We appealed to the DC Circuit and in 2014, the court upheld Judge Collyer's decision. At that point, satisfied with the court's answer, we chose not to proceed with an en banc or Supreme Court appeal.

General Concepts of Stem Cell Safety and How They Intertwine With Regulation

There has been a general opinion among members of the academic community that stem cells are unsafe until proven otherwise. However, despite this, there is quite a mounting database that demonstrates a robust safety profile for adult stem cells. As an illustration, if we just focus on orthopedic use, our safety studies with culture expanded stem cells show an excellent safety profile for MSCs in $n = 227$ and later $n = 339$ [19,20]. In addition, an independent meta-analysis of our source data by European researchers showed better safety for cultured MSCs than FDA-approved drug alternatives [21]. Finally, many others have published on long-term safety of expanded MSCs used to treat orthopedic conditions [21,22]. More recently, Hernigou published a very large dataset of approximately 1800 patients treated with same-day isolated bone marrow concentrate, rich in MSCs, showing no evidence of neoplasm across thousands of magnetic resonance images and x-rays [23].

Another aspect of safety concerns may be that whereas the cells are safe, their processing may introduce contaminants. Although a mass-produced cell line in which thousands of doses may be produced in bioreactors may cause a magnified safety problem (ie, contamination in a culture system may be distributed to many patients), for autologous cells that are singly processed, the risk is different. In the latter case, each cell treatment is obtained from a single person, who is consented for the risks and benefits of that procedure. Hence autologous cell therapies are more akin to the risk profiles of surgical procedures (such as bleeding, infection, etc.), which can be low or high risk depending on a variety of factors such as technical issues and anatomic concerns.

The Future?

One of the predictions made by many groups opposed to FDA regulation in the late 1990s was that these new regulatory restrictions would stall innovation and deprive patients of needed new cellular technologies. The Carticel experience is illustrative in this regard. Although in Europe, second- and third-generation cartilage procedures that involve cultured cells and biologic matrices have been approved, no other cell-based cartilage repair product has been approved in the United States since 1997 [24]. This is concerning because, in the United States, to date, no stem cell therapy has received FDA approval. This is despite 30,015 publications under the search term "mesenchymal stem cells" listed in the U.S. National Library of Medicine as of today's date [25]. In contrast, recent legislature in Japan has removed barriers to stem cell use through their new classification as a "regenerative medicine product." The revision of the existing Pharmaceutical Affairs Law allows the Japanese version of the FDA to grant a provisional approval on autologous stem cell therapies after a simple phase I-II trial while postmarketing surveillance continues. This new regulation is the first to formally recognize that "one off" autologous therapies have a safety profile more similar to medical procedures than mass produced prescription drugs [26].

Although the Regenerative Sciences decision was important in that it clarified the FDA's position that more than minimally manipulated cells used by a physician could be regulated as a drug, the decision also raises

concerns about the pace of innovation. To date, there is little concrete evidence that much of the peer-reviewed research on stem cells is clinically progressing into FDA-approved therapies. This may change in the future; however, it remains to be seen whether regulating physician care in the same manner as drug manufacturers will help or hurt innovation involving stem cell therapies.

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