Over the past decade, the number of stem cell therapy providers has dramatically increased. From what was once a rare and medically advanced procedure, stem cell therapy is now virtually as commonplace as getting a getting a flu shot. As the industry continues to grow however, what has the FDA done about regulation?

The FDA's overall scope of authority to regulate is limited to certain foods, drugs, biologics, medical devices, electronic products that give off radiation, cosmetics, veterinary products, and tobacco products. (Food and Drug Administration) Stem cells fall under drugs and biological products. Under these sections also exists human cell, tissue, and cellular and tissue-based products (HCT/Ps) which are regulated under 21 CFR 1271.

Under these meanings and regulations, the FDA currently only permits stem cell therapy procedures if they fall under the HCT/P exemption, which requires the stem cells to be no more than "*minimally manipulated* bone marrow for *homologous use."* Minimal manipulation is defined as "processing that does not alter the relevant biological characteristics of cells or tissues" and homologous use means the stem cells must be used clinically to do what they do *naturally* in a normal cellular setting rather than some other job that nature never intended them to do.

In 2008, the FDA began investigating Regenerative Sciences, LLC, which was performing a procedure known as Regenexx. The process of the procedure involved extraction of a person's samples of bone marrow and blood which were then sent to a lab for culturing and manipulation for a period of two weeks. While at the lab, the samples were given additives, nutrients, and were incubated to allow them to grow. The cells were then visually inspected, placed into syringes with additional fluids, and then re-injected into your body. Success from the

procedure varied and the treatments typically cost between $2,000 to more than $10,000 dollars depending upon the type of procedure performed.

A lawsuit ensued in which the FDA claimed that the procedure was a drug and biological product that did not meet the HCT/P 1271 exemption because it was more than minimally manipulated.

To meet the burden of proving that the Regenexx procedure was a drug, the FDA had to show that it was intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease. The FDA met its first burden by referencing Regenerative's own claims and admissions about the purpose of the Regenexx procedure, which was promoted to treat a variety of orthopedic conditions; advertised as an alternative to traditional surgery; and held out with the intent of treating diseases and injuries. The Court found that since the overall "intended use" of Regenexx was to treat patients, it was considered a drug.

The FDA then met the second burden of proving that the procedure was not exempted as an HCT/P under 21 CFR 1271. As the court noted, in order to qualify solely under the 1271 regulation, the HCT/P must be only minimally manipulated, meaning, "processing that does not alter the relevant biological characteristics of cells or tissues." The Court found that the Regenexx procedure resulted in "more than minimal manipulation of the HCT/Ps originally extracted from the patient" because the procedure involved "many steps" such as: 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. The Court also indicated that the FDA's conclusion that the procedure does not meet the regulatory definition of "minimal manipulation" is entitled to "substantial deference."

The Court's decision in this case was the first of its kind and is undoubtedly a step in the right direction for the regulation of stem cell therapy. However, how effective was the court in their ruling?

In their arguments to the Court, Regenerative pointed out a key issue—the ambiguity within FDA's regulations. In deciding the case however, the Court did not accept their position but rather, chose to give deference to FDA's interpretation of the definition. By doing so, an important consideration for the industry of stem cell therapy regulation is left in the balance.

Under 1271.3(d)(4), an item is not considered an HCT/P if it is "*minimally manipulated* bone marrow for *homologous use* and not combined with another article (except for water, crystalloids, or a sterilizing, preserving, or storage agent, if the addition of the agent does not raise new clinical safety concerns with respect to the bone marrow)." (Food and Drug Administration)

The two significant terms in this exception are "minimally manipulated" and "homologous use." Under 1271.3(f), the FDA has described minimally manipulated as:

> "(1) 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; and
>
> (2) For *cells* or nonstructural tissues, processing that does not alter the relevant biological characteristics of cells or tissues. "

In making its decision, the Court seemed to construe the regulation quite narrowly. However, as Regenerative suggested, the Court should have expanded its analysis and considered that some for room ambiguity may exist.

For instance, in terms of describing minimal manipulation as it pertains to stem cells in 1271.3(f)(2), the regulation essentially states that manipulation occurs when the "relevant biological characteristics of cells or tissues is altered." As noted above, a stem cell is an

"undifferentiated cell of a multicellular organism that is capable of giving rise to indefinitely more cells of the same type." The primary *characteristic* of a stem cell is its ability to divide amongst itself and regenerate into new cells in the body. The use of manipulation in stem cells, either minimally or otherwise, only relates to the *extent* of which the stem cell is *improved*, meaning that with any stem cell treatment, the stem cell itself is always being altered and undergoing change. Therefore, since the primary or *relevant characteristic* of a stem cell is to regenerate itself into a new cell, any sort of manipulation assisting in that process would be considered more than minimal, thus, calling for regulation under 1271.3(f)(2).

Homologous use was also not considered by the court. The term however, bears a significant importance in this case and along with minimal manipulation, could have made a substantial impact. The terms homologous use and minimal manipulation are only used once in entirety of 21 CFR 1271. They are both listed in the same regulation and are only words apart. The entirety of that regulation, 1271.3(d)(4), outlines the scope and gives the authority as to whether procedures like Regenexx must be regulated.

Homologous use is defined under 1271.3(c), which reads: "the 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." Homologous use can essentially be described as an HCT/P that is used clinically in a manner that is essentially the same as the natural endogenous function that is performed. In other words, in order for a stem cell therapy to qualify as "homologous use" they must be used clinically to do what they do *naturally* in a normal cellular setting rather than some other job that nature never intended them to do. (Knoepfler, Time to Bone Up On 'Homologous Use' In the Stem Cell Field)

Take for example the human body itself which has the *natural* ability to regenerate some of its own cells. For instance, skin cells usually replace themselves every two to three weeks and red blood cells recycle themselves about every four months. (Radford) This is a *natural* ability of the human body that is analogous to the meaning of homologous process. Now, consider again the general process of stem cell therapy whereby stem cells are extracted from your body, undergo manipulation, and are then transplanted back into your body. Could this be considered a *natural* or *basic function*? Alternatively, can a line actually be drawn to differentiate the two? Although arguments for both sides can be made, the Court

When considering the meaning of minimal manipulation the Court strictly gave deference to the FDA's meaning and limited its analysis to the regulation as it was written, while allowing no inference or bearing as to how it should be construed. In essence, the Court is leaving the future of stem cell therapy in the hands of eighteen words located in one definition. Furthermore, a look into the meaning of homologous use would have opened a whole new world of interpretation. Although the Court ruled in favor of the FDA, the ambiguity and vagueness left here will only work in favor of stem cell therapy providers.

Over the past decade, hundreds of stem cell therapy providers have entered the industry. Regenerative, as well as most of the other providers today, have taken great advantage of and capitalized on an unregulated industry. By allowing providers to work in a quasi-unregulated industry, not only will the advancement of stem cell research be hindered and seen in a more negative light, but the safety and effectiveness of the procedures will continue to be an issue

Take for example Dr. Zannos Grekos, who performed a stem cell treatment on a patient that suffered from pulmonary disease. As Grekos was performing the procedure, the patient began to experience cardiac arrest and eventually died. The procedure Dr. Grekos performed

was not approved by the FDA and he went undetected by authorities for many years. Luckily, the state medical board investigated him and eventually revoked his license.

In another example, Dr. Kenneth Welker also had his medical license suspended for performing unapproved stem cell therapy injections. The medical board viewed his practice as "an immediate danger to the public" because his injections caused adverse side effects to patients. What was more alarming were the statements made by Dr. Welker, who informed patients that his procedure could fix ailments ranging from arthritis and patellar tears, to vertigo. The clinic also advertised so called "miraculous patient stories" on their website and through social media. (Knoepfler, Perspectives on Emergency Suspension of Stem Cell Clinic Doc)

In addition to doctors like this, a trend of unscrupulous providers offering radical stem cell therapy treatments has been on the rise. These providers prey on the sick and vulnerable by claiming that their stem cell procedures could totally reverse their conditions and save their lives. In the most notable case, a provider known as Lawrence Stowe was found to have defrauded hundreds of thousands of dollars from patients suffering from severe and terminal illnesses. He falsely misrepresented himself as being a doctor and then convinced patients to undergo his *quack*-stem cell therapy treatments. None of his treatments were found to be effective and in some cases, caused more injury. Stowe was recently convicted and sentenced to five years in prison, and ordered to pay restitution to the tune of nearly half a million dollars to those that he deceived.

None of the procedures performed by these doctors had been regulated by the FDA. Despite the Court's decision, which sent a ripple through the stem cell therapy industry, doctors like this have continued to perform these unapproved, dangerous, and ineffective treatments. Although individual state medical boards have stepped in to investigate providers and suspend

their licenses, since the treatments are not regulated by the FDA, doctors could still face little to no liability as long as they can prove that their procedures constituted a valid form of the practice of medicine. Therefore, the danger of being barred from practicing medicine or the threat of going to prison has meant little when considering the cost versus benefit of performing these procedures. Hopefully the FDA, as well as the courts in deciding these cases, will take notice of the need for further refinement and regulation of the stem cell therapy industry.