Regenerative-Science FAQ's

Regenerative Sciences and the FDA - FAQs

What is the significance of this case?

This is a landmark legal case that will determine how doctors practice medicine for the next 20 years. Stem cells will be able to heal chronic and currently incurable conditions. If Regenerative's position is correct, adult stem cells will become body parts to be used by physicians to heal their patients-meaning the use of these cells will be the practice of medicine similar to how doctors now fertilize embryos in a lab to treat infertility. These assisted reproductive techniques (ART) currently are performed in physician owned labs using professional standards and guidelines, without FDA control. As a result, medical costs to use stem cells to treat disease will be much less and the control over how these cells are used will be between the doctor and the patient. If FDA is correct in its position, a different vision unfolds, where the patient's own stem cells are regulated as drugs and used like drugs. Costs to use these cells to cure disease will be dramatically higher and the federal government will dictate how, when, where, and why they are used.

What is the history of this case?

Regenerative Sciences has been using its patient's stem cells to treat orthopedic conditions since 2005. The practice received an untitled letter from the FDA in 2008 claiming its medical procedure was creating a new drug. Regenerative Sciences filed suit against FDA in 2008 and then again this year, to prompt the agency to declare how the FDA had the authority to regulate a medical practice, which Congress and the courts have always exempted from federal regulation. As recently as June, 2010, Regenerative Sciences was forced to file suit against FDA seeking a Temporary Restraining Order (TRO) to prompt the FDA to take "final agency action" or leave it's medical practice alone. Regenerative has been trying for two years to get the agency into a courtroom to answer to a federal judge why it believes it has regulatory authority over a medical practice. The agency's most recent action finally enjoining regenerative is the culmination of that two year effort by Regenerative and is welcomed by the company.

What is the medical procedure that the FDA claims is an "adulterated" and "misbranded" drug?

The Regenexx™ procedure involves taking the patient's own stem cells via a needle from the bone marrow, growing them in culture to bigger numbers, and then re-injecting them into the area in need of repair. It is only used for orthopedic problems like arthritis, tendon or ligament tears, or bulging lower back discs.

Why does the FDA consider these cells adulterated? What are cGMP?

cGMP (Current Good Manufacturing Practices) are federal drug mass manufacturing standards that would be used by a factory producing millions of doses of drugs as opposed to medical practices treating one patient at a time. The FDA is claiming that since these guidelines are not followed, the stem cells processed by Regenerative Sciences are "adulterated". FDA has never presented any evidence that any cells used by Regenerative's doctors are in fact "adulterated", but uses these drug regulation terms in its press release because Regenerative's medical practice doesn't follow drug factory guidelines.

Do medical clinics use cGMP drug mass manufacture guidelines?

No. Hospitals and medical clinics processing the patient's own tissue use a different standard called cGTP (good tissue practices). Surgical procedures don't use either standard, nor do medical clinics. In-vitro fertilization labs growing embryos (very similar to Regenerative's culture procedure) also don't use

cGMP guidelines, but instead professional guidelines promulgated by the College of American Pathologists. cGMP factory guidelines were designed to ensure safety when millions of drug doses are being produced and sent across the nation, not for medical clinics to administer to individual patients. Medical practices processing stem cells can also use ICMS guidelines (International Cellular Medicine Society). Regenerative Sciences already strictly adheres to the International Cellular Medicine Society's (ICMS) professional guidelines and has a third party, independent vendor check it's compliance.

Please respond to the comment published in the FDA release: "…When companies like Regenerative Sciences fail to comply with FDA laws and regulations, they put the public's health at risk."
Regenerative Sciences is not a threat to the public. Regenerative has published the world's largest safety study in adult stem cells currently indexed in the National Library of Medicine. This important study shows that their Regenexx™ procedure is dramatically safer than the more invasive surgical procedures it helps to replace. In fact, in the approximately five years that Regenerative Sciences has been operational, there have been no serious stem cell related complications in over 397 patients and 941 stem cell procedures. This is documented by the ICMS, a nonprofit patient safety and education organization, as well as the clinic itself. There have also been no reports or evidence of communicable disease transfer or of infectious disease introduction to patients.

How does the safety of this procedure compare to other common medical procedures?
The Regenerative Sciences cultured stem cell procedure (Regenexx™) has allowed many patients to avoid the need for joint replacement surgery. As an example, in a recent study by Regenerative Sciences, only 4% of patients who either needed a knee replacement or were told they would soon need one, opted for the knee replacement despite receiving the Regenexx™ procedure. Knee replacement procedures are invasive. For every 200 such surgeries performed in the U.S., one patient death will occur and 10-20 serious complications will result. Regenerative Science's innovative injection procedure has produced no such safety concerns.

Was Regenerative Sciences engaged in selling any cell products in "interstate commerce", which requires FDA jurisdiction?
No. Regenerative Sciences is a medical practice that only used its own patients cells in the same patient (autologous) at its facilities in Colorado.

What is the current action being taken by the FDA?
The FDA is seeking to enjoin Regenerative Sciences from practicing medicine using patient's own stem cells.

What is Regenerative's position on this action?
The FDA has twice declared that the clinic's therapeutic use of a patient's own stem cells, which are used to treat common orthopedic conditions, represent the manufacture of a new drug, which must come under federal control. Regenerative Sciences previously filed a suit in Denver District Court after a similar prior claim by the FDA, based on the fact that the regulation of medical facilities lies with the state and, as the FDA is a federal agency, they have no jurisdiction in the matter. In addition, Regenerative Sciences claims that the FDA's regulation making the patient's own stem cells a biologic drug is *ultra vires*, or beyond the power that congress granted the agency.

Will Regenerative continue offering procedures using the patient's own stem cells? What the FDA believes is a drug is the culturing of cells used by Regenerative Sciences to produce greater numbers of

cells for patient therapy. Regenerative Sciences counters that this is almost identical to other common medical procedures not under the FDA's control (like in-vitro fertilization). Regenerative Sciences has voluntarily decided to stop culturing cells until the legal case is decided, but it will still offer its patients same-day stem cell isolation procedures that are exempt from FDA regulations.

What is the projected timeline of events now that the FDA has taken action?
Regenerative Sciences will file its responses. The case may take a year or more to be decided in the judicial system.

What do Regenerative Science's patients say about the actions the FDA has taken?
Barbara James - Boulder, Colorado"I am extremely disappointed in the FDA's closed-minded thinking and disregard for patients who need pain relief."

Harold Kaye - Denver, Colorado"I am downright angry at this decision. The Regenexx™ procedure has changed my life. Before I met Drs. Centeno and Schultz, my life was plagued by physical pain. I was debilitated. I now have the strength and ability to live my retirement years as I have always wanted. It is sad that others in my situation may not get the chance to get this treatment here in the US, but it doesn't surprise me that the Federal Government could be so short-sighted."

If you have additional questions, please contact Jennifer Kardian at 678-352-3652 or jkardian@sjonespr.com.

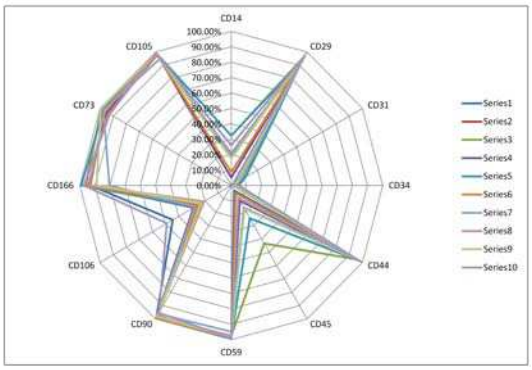
More detailed science on Regenerative medical procedure:

Basic Description of Regenerative's Cultured Autologous Stem Cell Procedure: Regenerative's doctors take a bone marrow aspirate from the PSIS area of the hip, extract approximately 60-90 cc of marrow aspirate and send this to their lab for processing. The lab isolates a buffy coat and plates this in monolayer culture flasks with autologous platelet lysate (the patient's own growth factors derived from the patients whole blood). The cells are culture expanded approximately 100X over 2-3 weeks and further isolated to a pure mesenchymal stem cell (MSC) population. This process is very similar to the 5 day blastocyst procedure used by in-vitro fertilization labs which are <u>not</u> FDA regulated.

The cultured MSC's are then placed in a syringe and imaging guidance (real time fluoroscopy or musculoskeletal ultrasound) is used to accurately inject the cells into the area of the musculoskeletal system in need of repair.

How does Regenerative know it is injecting MSC's? The graph below demonstrates common surface antigens on the cells grown with Regenerative's procedure that are consistent with patterns commonly seen on MSC's.

Surface Antigen Expression using Flow Cytometry for 10 MSC Lines Grown with Regenexx Procedure



Regenerative Sciences

How does Regenerative protect patient safety?

Regenerative follows International Cellular Medicine Society lab guidelines. These are similar to cGTP (good tissue processing practices) with specific items tailored to stem cell and other cellular processing. An independent third party auditor is hired every 6-12 months to ensure that these guidelines are being followed and whether process improvements should be made. These guidelines are most similar to the College of American Pathologists (CAP) guidelines for in-vitro fertilizations labs. Other analogues include the pharmacy guidelines followed by compounding pharmacists. What all three guidelines sets have in common is that they are designed for appropriate safety in processing one patient's tissue at a time. They are not drug mass manufacturing guidelines (cGMP), which Regenerative feels would not measurably increase or ensure patient safety. cGMP guidelines are tailored to the safe manufacture of millions of doses of medicines and as such assist in the public health tracking of "bad batches" of medications.

More details on Regenerative's use of cultured cells-

-IRB Approved Research-Regenerative spent from 2005-2007 in IRB approved research (S.I.F. IRB-HHS registration Spinal Injury Foundation-IRB00002637).

-**Animal modeling**: Well before we started our IRB approved study in 2005 and since, there are many studies showing proof of concept that MSC's assist in cartilage healing and joint repair, see http://tiny.cc/nka02 (this is a brief PubMed search on the topic).

-**MSC's are well vetted**-As of this morning there are 11,837 studies on MSC's listed in PubMed. Compare that to a search on "natural killer t cells" which yields 9,879 studies. Meaning we know huge amounts about MSC's at this point.

-**Clinical translation of MSC's by others in orthopedics**: Wakitani (Japan) has published on an 11 year follow-up of 40 patients treated with MSC for orthopedic knee applications. A recent

paper out of Singapore (n=72) shows the same. At 2 year follow-up, patients who had their knees surgically treated with MSC's showed lower morbidity than those who received surgery alone.

-**Our safety data**. Regenerative has published the world's largest safety study to date on the use of MSC's in orthopedics (n=227).

Regenerative has also recently submitted for peer review an n=339 paper with more than 200 serial 3.0T MRI's of re-implant sites (available on request). The following highlight from Regenerative's most recent paper is important:

> *We believe that it is important to compare our complications data to traditional orthopedic surgery risks. A recent outcome analysis of our knee OA patients is illustrative. Almost all of these patients were advised by medical professionals that they were either a current candidate for knee replacement or would soon need a knee arthroplasty. Over the observation period, only 4.1% reported during routine complications tracking data gathering that they opted for knee replacement despite MSC treatment. A recent retrospective study of more than 17,000 total knee arthroplasties (TKA) demonstrated that serious surgical complications were between 7.7%-10% (primary vs. revision; p=0.007). 90 day complication rates for death were 0.3% and 0.6% (p=0.1) and for pulmonary embolism 0.4% and 0.5% (p=0.6). 90 day re-admission rates for primary and revision TKA including infection were 0.5% and 4.2% (p<0.001).[25] Applying these surgical complication rates to our 374 knee procedures discussed in this paper would yield the following complications:*
> *1. 29-37 patients with serious surgical complications, 2. Approximately 1-2 mortalities as a result of the procedure, 3. Approximately 2 patients with pulmonary emboli*
> *4. Approximately 2-16 patients with a hospital readmission for serious infection (IV antibiotics)*
>
> *In our dataset for knee procedures, none of these serious complications were adjudicated as likely caused by the MSC procedure.*
>
> *[25]-Khatod, M., et al., Knee replacement: epidemiology, outcomes, and trends in Southern California: 17,080 replacements from 1995 through 2004. Acta Orthop, 2008.* ***79****(6): p. 812-9.*

Summary-If the patients in Regenerative's most recent paper had undergone knee surgery instead of the stem cell injection, they would have had substantially more morbidity and mortality. It's important to note that only a handful of Regenerative's patients either had only Mild or Moderate HHS level complications (problems that were either self-limited or could be remediated with simple therapeutic measures).

-**Objective data**: Regenerative has published several studies that show proof of concept that MSC injections using Regenerative's procedure that demonstrated increased the size of meniscus and chondral cartilage when measured on 3.0 T MRI.

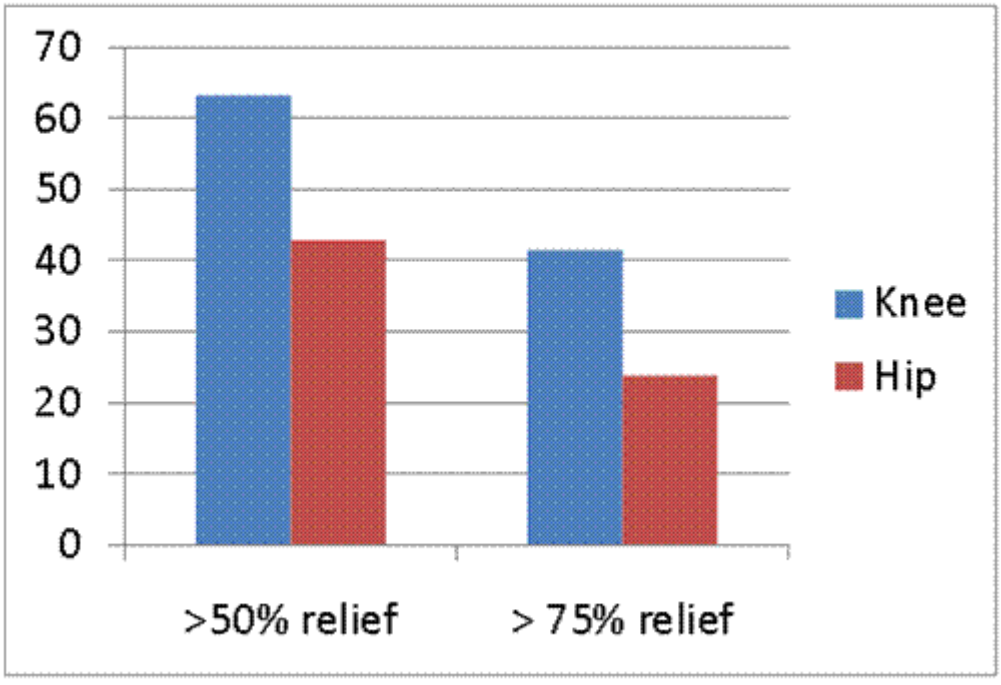
Additional before/after case studies using 3.0T MRI and showing objective evidence of positive effects of the treatment are available on request.

-Subjective data: Regenerative has recently completed data analysis for a knee and hip osteoarthritis paper that will be submitted for peer review in the next 1-2 months. This utilized a prospective, untreated control. To highlight some data from this knee/hip paper:

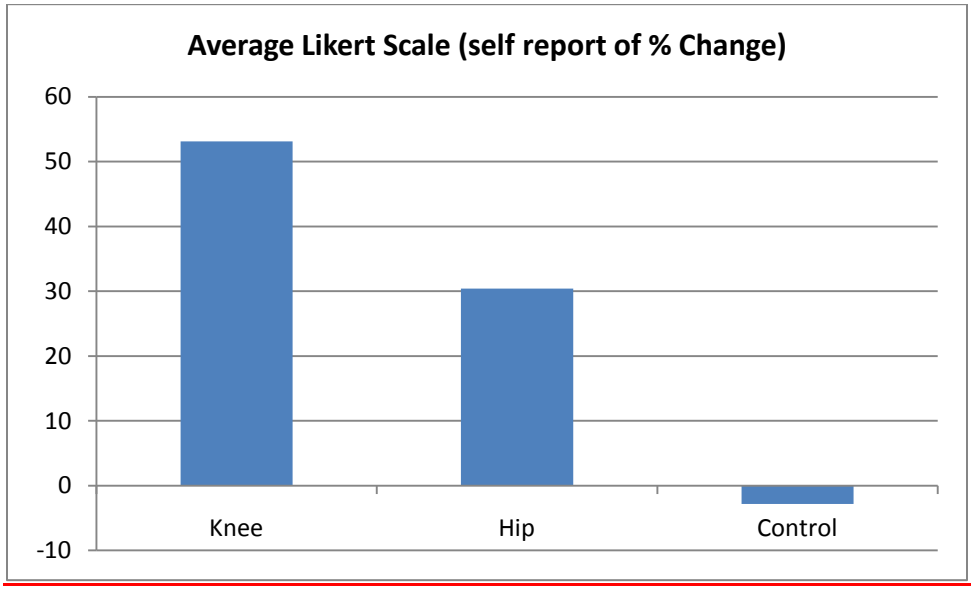
> *Average reported relief at 53.12% in the knee OA group (n=133 reporting) and 30.35% in the hip OA group (n=42 reporting), this is a significant difference between the groups (p=0.003, equal variances assumed). In addition, the comparison to the control group is significant (p=1.608E-15, equal variances not assumed), with that group reporting an average -2.75% change. There were n=29 patients (n=6 for hip, n=23 for knee) surveyed in the control group who were on average 1.07 years out from their first request for information.*

Below in figure 7 is reported relief levels of hip and knee groups:

Figure 7: The percentage of patients reporting >50% relief and >75% relief for knee and hip groups.



Below is a second graph showing average relief in treated knee patients, hip patients, and an untreated control group.



While without a placebo control, all reported changes in outcome may have been due to placebo responses. However, while that may explain the significant difference between the prospective untreated control and the knee group, it doesn't explain the difference in outcome between the knee and hip groups (i.e. there is no data that supports that a group of hip OA patients are more susceptible to placebo conditioning than a group of knee OA patients). As a result of this data, while Regenerative has had hip patients with significant responses, this data analysis has prompted the physicians to reduce the number of patients placed in the GOOD category for hip procedures.

-**Medical Innovation**-There are two different approaches to medical discovery. The first is the placebo RCT. The upside is that it provides big statistical firepower, the downside is that it's inflexible and the data only generalizes to patients that meet the inclusion/exclusion criteria of the study. The other downside is that the extreme expense limits medical innovation, i.e. only treatments with robust business plans can be tested in this fashion. The second method is physician practice. Physicians note problems with treating patients, solve those problems responsibly by reviewing risk/benefit with the patient and try new approaches to therapy. This process starts with case reports, moves to case series, and then to controlled trials, and finally to P-RCT's. For example, a search of PubMed shows 1.5 million results for the term "case study", 56,000 results for "case series", 460,000 for "controlled trial", and 85,000 for "randomized placebo controlled trial". In this search, case study data outnumbered controlled trial data by 3 to 1. There is societal benefit to this discovery pathway. This is what the federal court judge in U.S. vs. Evers stated (FDA went after Evers for using drugs off label and indication- *(United States v. Evers*, 453 F. Supp. 1141, 1142 (M.D. Ala. 1978)):

The court agreed with Dr. Evers stating "Congress did not intend the Food and Drug Administration to interfere with medical practice as between the physician and the patient."[4]

The court went on to explain why the FDA should not interfere with the practice of medicine. In its opinion, the Court noted that a drug's package insert is well-reviewed and informational, but it is not the most up-to-date information on the drug's uses.[5] *New uses are often discovered, reported through medical journals or seminars, and may become widely used in the medical profession; however, the drug manufacturer may not have sufficient financial or other interests to pursue FDA approval for the new uses.*[6] *Further, if a doctor must prescribe and treat only within "federally sanctioned" methods, this would result in medical stagnation at the best, as physicians await drug manufacturers' initiative and FDA approval.*[7] *The court reasoned, "A free, progressive society has an enormous stake in recognizing and protecting this right of the physician."*[8]

-**Investigational Care**-Our practice sees an important benefit to offering investigational care. Investigational care is all around us. Investigational care occurs every time a doctor orders a new compounded formulation based on a research article that he or she read and thought was credible, every time a physician uses an FDA approved drug off-label or off-indication, every time a doctor tries a tried and true surgical procedure in a new way to try and improve patient outcomes. Should patients have the right to access investigational care outside of a sponsored trial? There are certainly right and wrong ways to allow access to such care. International Cellular Medicine Society guidelines allow for slow and measured access to investigational care using cultured stem cells. This includes IRB approval in the early stages, detailed, prospective, third party complications tracking, etc...

Are stem cells body parts or drugs? We would caution against "stem cell exceptionalism". For example, the 5 day blastocyst procedure used by fertility specialists as part of in-vitro fertilization is not FDA regulated, doesn't use drug manufacture laboratory guidelines, and is considered the physician practice of medicine. Setting off stem cells as a separate category just because those cells are important to the biopharma industry doesn't help patients get to cures any faster or make stem cells safer.

The position of Regenerative (just like the federal judge who recently decided the BRCA gene case-see http://wellness.blogs.time.com/2010/03/30/court-rules-against-patenting-human-

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[4] *Id.* at 1149 (citing 37 Fed. Reg. at 16503 (Aug. 15, 1972)).

[5] *Id.* at 1149.

[6] *Id.* at 1150.

[7] *Id.* (quoting *People v. Privitera*, 141 Cal. Rptr. 764, 774 (1977)).

[8] *Id.*

genes/), is that stem cells-cultured or not are body parts and represent a set of tools for doctors to use responsibly to help patients. FDA's and the pharmaceutical industry's position is that they are drugs.