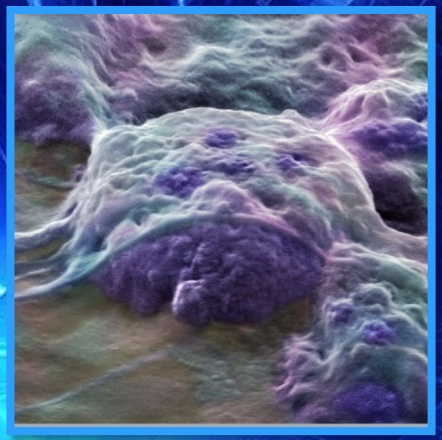
2021

FDA REGULATION OF REGEN MED THERAPIES



BRIAN J. SHIPLE, DO, CAQSM, RMSK

PRESIDENT AAOM

THE CENTER FOR SPORTS MEDICINE

PHILADELPHIA, PA

EMERGING NEW FIELD BUT STILL A TODLER…

- Regenerative medicine technologies for orthopedic medicine application has produced basic science and clinical research in investigating the use of stem cells in several areas including, but not limited to:
  - Osteoarthritis - 1,2
  - Articular cartilage repair,3,4
  - Anterior cruciate ligament (ACL) reconstruction,5–8
  - Tendon healing,9–12
  - Meniscus regeneration.13–15

References

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FDA Primer

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- As of 2017, 3/4th of the FDA budget (approximately $700 million) is funded by the pharmaceutical companies due to the Prescription Drug User Fee Act.
- FDA- ensures the safety and efficacy of drugs and medical devices for the the public and ensures the safety of drugs and medical devices being transferred across state lines.

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- The U.S. Congress is also considering similarly proposed legislation and in August of 2017, the U.S. Senate passed S. 204, Trickett, Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017.

The 21st Century Cures Act

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- In regards to Regenerative Medicine, the Act amends Section 506 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356) by requiring Expedited Review for regenerative medicine therapies, including human cells and tissues, intended to treat, modify, reverse, or cure a serious or life threatening disease or condition, where there is preliminary clinical evidence indicating that the drug has the potential to address unmet medical needs.

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- There are also ongoing efforts at the federal level to ensure even greater access to treatments that are not subject to FDA approval prior to administration to patients.

FDA Drafts/ Guidance

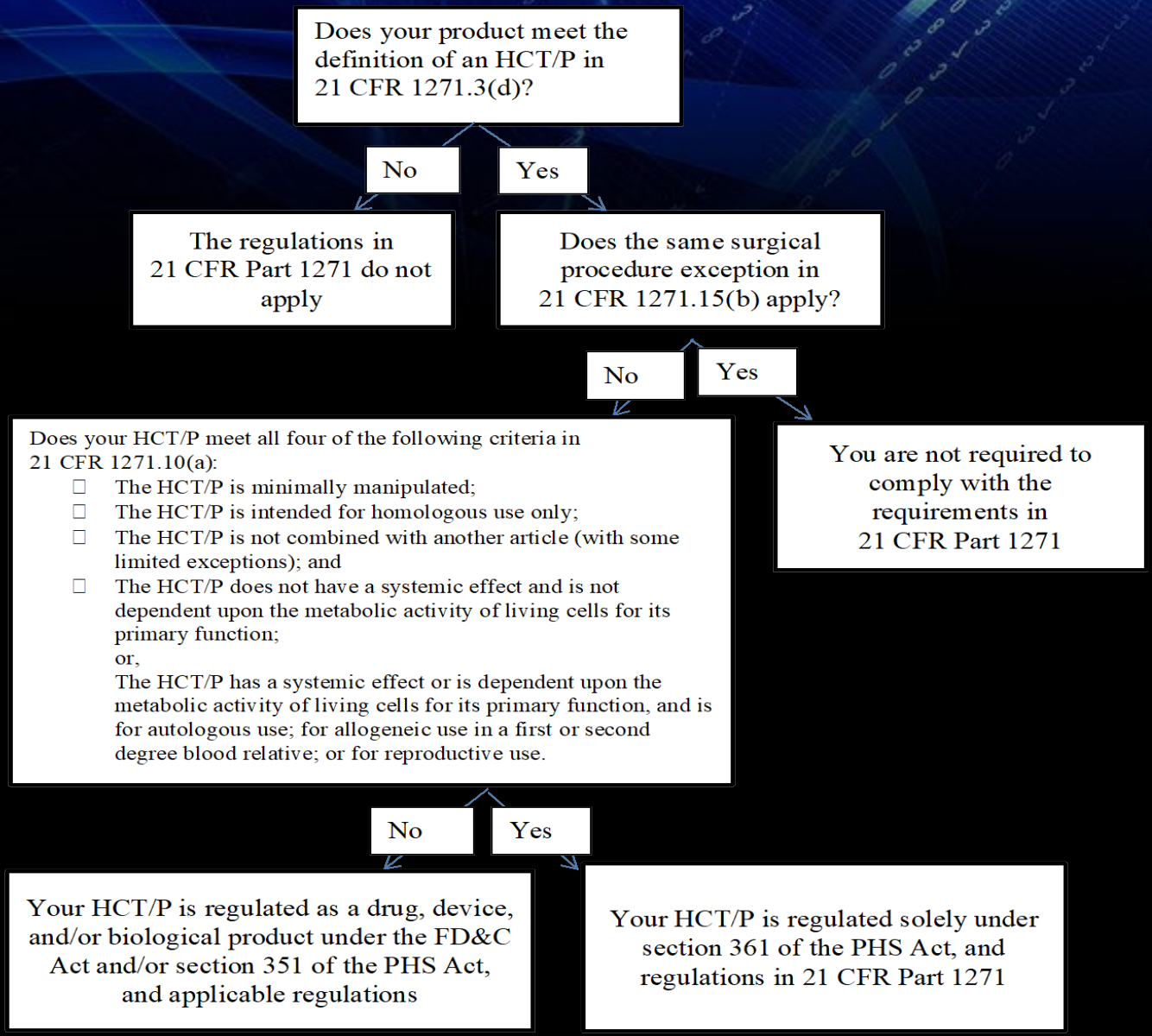
- **Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use**
- **Guidance for Industry and Food and Drug Administration Staff**
- Nov 2017
- All draft docs from 2014-17 were finalized in this 2017 document
- In 2020 the guidance documents became laws. The 3.5 year review and comment period from 2017 to 2021 was a period of time that our industry was given to prove to the FDA that our products were safe and efficacious.
- Enforcement of these laws over how we operate and treat our patients were delayed due to Covid-19. As of June 1st the review period is over and CEBER published it's letter to the public on June 3rd ,2021.

FDA Drafts/ Guidance

- FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word "*should*" in FDA's guidances means that something is suggested or recommended, but not required.

Regen Med FDA Compliance Flow Chart

Flowchart to illustrate how to apply the criteria in 21 CFR 1271.15(b) and 1271.10(a)



HCT/P

- HCT/Ps are defined in 21 CFR 1271.3(d) as Human Cells, Tissues, and cellular and tissue-based Products.
- They are articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient.

HCT/P

- Under the authority of section 361 of the Public Health Service (PHS) Act, FDA established regulations for HCT/Ps to prevent the introduction, transmission, and spread of communicable diseases.
- These regulations can be found in 21 CFR Part 1271.

HCT/Ps

- HCT/Ps are Articles containing bone, ligament, skin, dura mater, heart valve, cornea, adipose, hematopoietic/progenitor cells derived from peripheral and umbilical cord blood vessels, manipulated autologous chondrocytes, epithelial cells on a synthetic matrix, semen and other reproductive tissue, amniotic membrane and umbilical cord, articular cartilage, tendon

Not an HCT/P

- The following articles are not considered HCT/Ps:
  - Whole blood or blood components or blood derivative products subject to listing underpart 607 and 207 respectively. ie, PRP
  - Minimally manipulated bone marrow for **homologous** use and **not combined with other 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. ie, BMC

1271.15b (ie, FAT Grafting)

- Title 21 of the Code of Federal Regulations (CFR) Part 1271, specifically the exception set forth in 21 CFR 1271.15(b).

- The FDA's view is that autologous cells or tissues that are removed from an individual and implanted into the same individual without intervening processing steps beyond rinsing, cleansing, sizing, or shaping, raise no additional risks of contamination and communicable disease transmission beyond that typically associated with surgery. FDA considers the same surgical procedure exception to be a narrow exception to regulation under Part 1271

1271.15b (ie, FAT Grafting)

- For the same surgical procedure exception to apply, an ESTABLISMENT must:
  - a. Remove and implant the HCT/Ps into the same individual from whom they were removed (autologous use)
  - b. Implant the HCT/Ps within the same surgical procedure
  - c. The HCT/Ps remain “such HCT/Ps;” they are in their original form (Minimal Manipulation)

1271.15b Example

- Example 7-1: Adipose tissue is recovered by tumescent liposuction. The lipoaspirate is centrifuged to facilitate removal of debris and extracellular fluid.
- No steps are taken to isolate stem cells (also commonly referred to as stromal vascular fraction) from the lipoaspirate. The adipose tissue remains “such HCT/P” because nothing else is added to the adipose tissue, only minor handling is performed, and the adipose tissue retains its original form as a connective tissue composed of clusters of adipocytes and other cells surrounded by a reticular fiber network and interspersed small blood vessels.
- It is then re-implanted into the same patient from whom it was removed in order to achieve the intended effect.

Example 1271.15b

- Example 7-2: Adipose tissue is recovered by tumescent liposuction and processed (ie, enzymatic digestion, mechanical disruption) to isolate cellular components, commonly referred to as stromal vascular fraction, which is considered a potential source of adipose-derived stromal/stem cells. Cell isolation would typically cause the adipose tissue to no longer be “such HCT/P” and the establishment would generally not be considered to qualify for the exception under 21 CFR 1271.15(b)

Section 361 (BM, Fat or Placental Products)

- HCT/Ps are currently regulated under Sections 351 and 361 of the Public Health Service Act. However, an HCT/P can be regulated solely under Section 361 of the PHS Act if it meets the following 4 criteria:
- 1. Minimally manipulated
- 2. Intended for homologous use only
- 3. Not combined with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent
- 4. Either:
  - a. Does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or
  - b. Has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and is for autologous use, use in a first or second degree blood relative, or reproductive use.

351 versus 361

- The difference between an HCT/P that is regulated under both sections of the Public Health Service Act, as opposed to solely under Section 361, is significant for providers of stem cell treatments

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- Under Section 351 the requirements for premarket authorization of a product are much more stringent and require conducting clinical investigations under an investigational new drug (IND) application and obtaining a biologics license (BLA) through the FDA.

351 versus 361

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- Under Section 351 the requirements for premarket authorization of a product are much more stringent and require conducting clinical investigations under an investigational new drug (IND) application and obtaining a biologics license (BLA) through the FDA.

- Under Section 361 the requirements focus only on the prevention of communicable diseases. This represents a lower regulatory threshold for HCT/Ps; their use and transplantation **Could Be** considered to fall under the practice of medicine and would therefore be regulated by state medical boards

Section 351's Extensive Regulation of HCT/Ps as Biologics and Drugs

- Products are most likely to shift from the comparatively relaxed oversight of Section 361 to the more stringent requirements of Section 351 if—at least in the FDA's view— they present greater risks. While Section 361 focuses on safety and preventing infection and disease transmission, Section 351 concentrates on both safety and effectiveness.

Section 351's Extensive Regulation of HCT/Ps as Biologics and Drugs

- For the clinician, this imposes more onerous requirements (such as cGMPs and premarketing approval) with little distinction between individuals and small physician practices versus larger pharmaceutical industries. Thus, cells or processing methods that fail to satisfy any of Section 361's requirements will cast a product into the heavily regulated 351 regs

Section 351's Extensive Regulation

- A product will fall within Section 351 if it is one or more of the following:

1. More than **minimally manipulated**, which for cells and nonstructural tissue means to present a risk of change in cell morphology, function, expression, or other relevant biological characteristics during processing, storage, etc.
2. Used for a **nonhomologous** purpose.
3. **Combined with other articles** that may pose additional concerns regarding clinical safety.
1. Have a **systemic effect** or otherwise rely on the metabolic activity of living cells for its primary function, and be used in a context other than autologous use, allogeneic use in a first or second degree relative, or reproductive use.

Compliance with 351

Section 351:

- Must register and file a list of each HCT/Ps with CBER each year.
- Must obtain formal premarket approval from the FDA. This involves submitting an IND !!! (Investigational New Drug Application), Biologics License Application (BLA), or, when dealing with a 510k medical device, a premarket approval application or premarket notification.
- Costly and time-consuming controlled trials to establish product safety,

• purity, potency, efficacy, and stability.

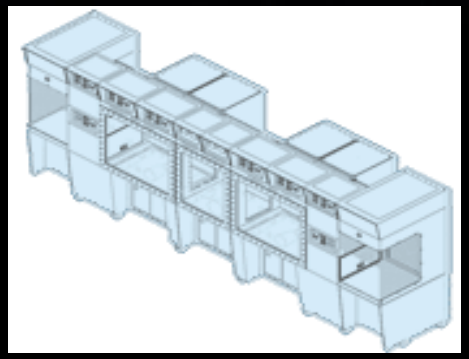
- Also must follow GMP standards which includes prescription drug labeling requirements similar to major pharma.
- Without this, the product will be considered “adulterated” and /or “misbranded.” as per FDA and PHSA.
- This is true even using autologous cell preps !!!

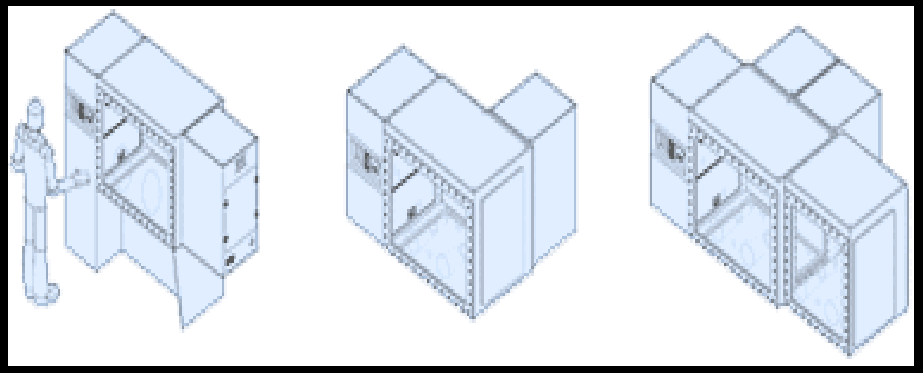
• FDA can sanction you, shut you down

- US v. Regenerative Sciences, LLC, 741 F.3d1314 (D.C Cir. 2014)

Office based GMP… ?

- It may be possible
- It will be expensive





Minimal Manipulation

- FDA (argues that it) has the authority to regulate anything beyond minimal manipulation and homologous use:
- Minimal Manipulation: minor processing including purification, centrifugation, washing, preservation, storage
  - 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
  - For cells or nonstructural tissues, processing that does not alter the relevant biological characteristics of cells or tissues.

Minimal Manipulation Example

- Example 10-2: Original relevant characteristics of amniotic membrane relating to its utility to serve as a barrier generally include the tissue's physical integrity, tensile strength, and elasticity.
  - A manufacturer processes amniotic membrane to preserve it and package it in sheets. The HCT/P generally is considered minimally manipulated because the processing does not alter the original relevant characteristics of the HCT/P relating to its utility to serve as a barrier.
  - A manufacturer grinds and lyophilizes amniotic membrane and packages it as particles. The HCT/P generally is considered more than minimally manipulated because the processing alters the original relevant characteristics of the HCT/P relating to its utility to serve as a barrier.

SVF- Stem Cell Prep

- Example 14-1: Original relevant characteristics of adipose tissue relating to its utility to provide cushioning and support generally include its bulk and lipid storage capacity. A manufacturer recovers adipose tissue by tumescent liposuction and processes (e.g., enzymatically digests, mechanically disrupts, etc.) the adipose tissue to isolate cellular components (with or without subsequent cell culture or expansion), commonly referred to as stromal vascular fraction, which is considered a potential source of adipose-derived stromal/stem cells. The definition of minimal manipulation for structural tissue applies. This is more than minimally manipulated.

Homologous Use

- Homologous Use: 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 including when such cells or tissues are for autologous use.
  - Recipient cells or tissues that are identical (e.g., skin for skin) to the donor cells or tissues, and perform one or more of the same basic functions in the recipient as the cells or tissues performed in the donor; or
  - Recipient cells or tissues that may not be identical to the donor's cells or tissues, but that perform one or more of the same basic functions in the recipient as the cells or tissues performed in the donor.

Fat Homologous Use Examples

- Adipose tissue is used to fill voids in the face or hands (e.g., for cosmetic reasons). This is homologous use because providing cushioning and support, is a basic function of adipose tissue.

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- An HCT/P from adipose tissue is used to treat musculoskeletal conditions such as arthritis or tendonitis by regenerating or promoting the regeneration of articular cartilage or tendon. This is generally not considered a homologous use because regenerating or promoting the regeneration of cartilage or tendon is not a basic function of adipose tissue.

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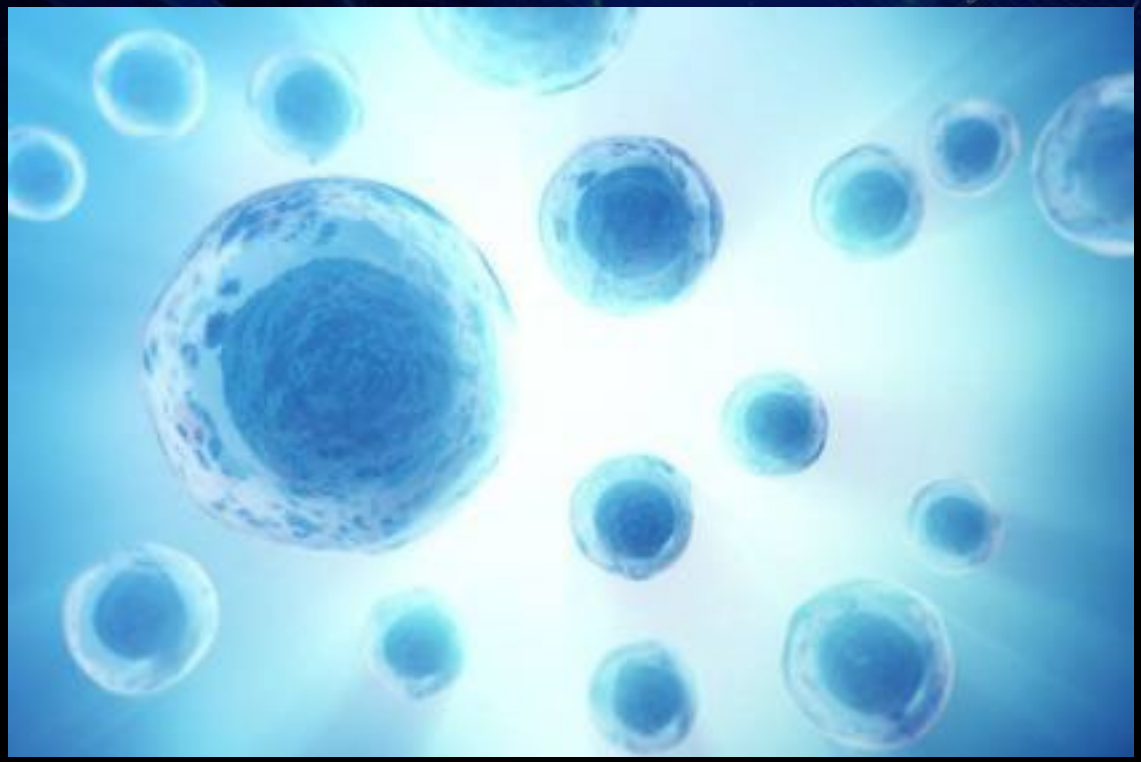
- Adipose tissue is used for transplantation into the subcutaneous areas of breast for reconstruction or augmentation procedures. This is homologous use because providing cushioning and support is a basic function of adipose tissue.

Important Patient and Consumer Information About Regenerative Medicine Therapies



June 3, 2021

“The US Food and Drug Administration (FDA) regulates regenerative medicine products.

There continues to be broad marketing of unapproved products considered regenerative medicine therapies that are intended for the treatment or cure of a wide range of diseases or medical conditions.

These products require FDA licensure/approval to be marketed to consumers.

Before approval, these products require FDA oversight in a clinical trial.

These unapproved products whether recovered from your own body or another person’s body, include stem cells, stromal vascular fraction (fat-derived cells), umbilical cord blood and/or cord blood stem cells[1], amniotic fluid, Wharton’s jelly, ortho-biologics, and exosomes.

FDA has received reports of blindness, tumor formation, infections, and more, detailed below, due to the use of these unapproved products.”

Please know that if you are being charged for these products or offered these products outside of a clinical trial, you are likely being deceived and offered a product illegally.

FDA has repeatedly notified manufacturers, clinics, and health care practitioners of the need for Investigational New Drug applications (INDs) to legally administer these products and to ensure safety measures are in place prior to administration."

1271.15(b)

- Same Day Surgical Exemption
- One of the AAOM Board members decided to apply for an IND about the time the pandemic started.
- He applied for an IND to CEBER for a license to treat knee O/A with Bone Marrow Aspirate

Post June 3rd

- He has had many weekly meetings with the head of CEBER, Peter Marks, MD
- In these meetings he has represented us the AAOM and asked some very strait forward questions since June 3rd after the FDA came out with their letter to the public published on their web site.

Is Fat in MSK Regen Med Legal?

- One question, referred to fat grafting and Homologous use. Is it FDA compliant to implant a simple fat graft into a joint or tendon? Answer: 'No, it's non-homologous use of the HCT/P and fails the 361- exemption test. Fat does not reside in articular joints or tendons in it's native state.'
- In order to pass the 361-exemption test it must be like-to-like, ie, ass to face transfer for cosmetic facial filling to fill a void from, ie, cancer surgery. Or ass to a calcaneal fat pad for fat pad syndrome.

Is Bone Marrow in MSK legal

- Dr Marks was asked the same question about Bone Marrow which under 1271.3(d) is actually, not considered an HCT/P as long as it not more than minimally manipulated or used in a non-homologous way. He said because bone marrow is from bone, bone to bone is compliant. IE, BMC implanted in a chronic fracture site, AVN or an OCD are all compliant.

Same Day Surgical Exemption?

- Bone Marrow transferred to a joint or tendon is not like-to-like and therefore fails the homologous use test and is considered a 351 drug.
- What about 1271.15(b) Same Day Surgical Exemption and 1271.3(d) Not an HCT/P?
- Dr Marks told our board member he would like to see BM preserved in the OR under sterile conditions. He promised to get back to him with something in writing.

Homologous use of BMC- Safe

- For now the important facts about bone marrow are this:
- 1. Bone Marrow is not an HCT/P as long as it is minimally manipulated and it's intended use is Homologous
- 2. Bone-to-Bone-I/O or probably bone to tendon or ligament attachment (enthesis) are all homologous use and compliant

BMC in Joints and Soft Tissue

- Bone Marrow to joints or tendons or muscles is **non-homologous** and BM becomes an HCT/P and then it FAILS the 361 Exemption Test.
- So for these important indications that IROM docs have used for years, BM becomes a 351 drug and needs a BLA in order to use it legally.

Will BMC be exempt under 1271.15(b)?

- Dr Marks said he would like to see the use of BM in sterile conditions preserved like in an OR and would get back to us in writing for clarity on this issue
- In the opinion of our board member after more talks with Dr. Marks on this topic there is some conflict between different sections of the FDA on these topics and the request for clarity has not been forth coming as-of-yet.

Will Fat be exempt under 1271.15(b)

- Bottom line- Fat transfer in plastic surgery is compliant under 361 Homologous use exemption.
- If fat is transferred to most MSK indications, Ass to joint, it is a 351 drug.
- What about 1271.15(b) Same Day Surgical Exemption?
- Dr Marks has not remarked on 1271.15(b) and whether the Same Day Surgical Exemption test could be applied to a non-homologous fat transfer

Compliance with FDA Law

- What can we do to stay out of trouble?
- Or a better way to say this- to stay compliant w/ the FDA?
- Remove any reference on your web sites and marketing to the words Stem Cells and Regenerative Medicine.
- Remove terms like cure and heal in reference to the intended action of our treatments.

Federal Trade Commission

- What can you say in your advertisement and web sites and blogs to keep your practice safe?
- You can say you treat, help, may help.
- You can quote studies that your treatment protocol follows or mimics.
- Rather than saying your product is a stem cell product, call it what it is, a bone marrow concentrate or bone marrow aspirate.

Legal use of a 351 HCT/P

- Going forward you will need to be licensed by the FDA after applying for and receiving an IND to study an HCT/P under an FDA approved and IRB approved study to show safety and efficacy. Then if both safety and efficacy are proven you may apply for a Biologic License to use the HCT/P “drug” in your patients and market the new “drug” for it’s indication legally.

Legal use of non-HCT/Ps

- So what's left in our tool-box?
- PRP is not an HCT/P and CEBER has said it is compliant, for now…
  - As long as you make it with 510K approved products. According to CEBER
- Dextrose is not an HCT/P
- Bone Marrow and BMC are not HCT/Ps as long as it's used in a Homolgous way, i.e.- Bone-to-Bone is compliant
- Fat transfer to a fat pad is still OK

Placental Tissue Products

- What is gone- for now?
- Placental Tissue products.
  - Amniotic products used in sheets to cover wounds and wrap structures is homologous and is still compliant
  - Amniotic products that have been turned into a powder by morselization is more than minimally manipulated and is a 351 drug

Exosomes

- Exosomes- more than minimally manipulated as they come from culture expansion from human Bone Marrow or Umbilical Cord Blood derived MSCs
- There is one Exosome product that comes from Amniotic Fluid and in theory is not more than minimally manipulated but would have issues with homologous use to qualify for a 361 exemption

The Only License to use UCB

- Umbilical Cord Blood- at least one product has an IND/ BL for a medical indication dealing with hematopoetic progenitor cells derived from UCB to produce blood cells.
  - There are no other approved indications and all other Umbilical Cord and Cord Blood Products are considered 351 Drugs
- Amniotic Fluid-is a 351 Drug

Beware of Placental Tissue Companies

- Wharton's Jelly- is the interstitial tissue that resides between the Umbilical Cord covering and it's blood vessels. It is rich in MSCs and Hyaluronic acid among other good things. It is a 351 Drug as well.
  - One company claims they have the only Government approved Wharton's Jelly product and is marketing it hard, still to our practices…

To Good to be True?

- Wharton's Jelly- Approved by the FDA?
- In their advertising they reference their approval. So, I looked it up.
- The information supplied shows their product applied to CMS and achieved a Q-code for Medicare reimbursement. Which is a big deal for the company.
- But, getting a Q-code from CMS and getting a Biologic License from the FDA to legally market their product as a drug are not the same!

Q-Codes

- Q-codes given to tissue companies has allowed some Placental Tissue products to be used successfully in certain fields like wound care and orthopedics and these doctors and hospitals have done nothing wrong. Medicare has even reimbursed them to use these products with the approved Q-Code.
- As of June 1st these products changed from 361 to 351 Drugs and now are not legal to use, without a Biologic License from the FDA.

Say Good-Bye to Q-Codes

- Q-codes allowing reimbursement for non-approved Regen Med products according to CEBER will be removed from CMS and Medicare soon. Beware…

Certification

- What can we do as an organization to become compliant with the FDA/ CEBER?
- We can develop training programs that lead to certification as a physician that demonstrates to the public, our physician community and the FDA that we are competent to use these HCT/Ps and other products like PRP safely and with efficacy
- See Rep Fred Upton's letter to CEBER

Who should perform these procedures?

- The FDA/ CEBER has recommended that we, (AAOM) should only train physicians that have completed a residency program as a minimum bar or threshold to practice with these HCT/Ps.
- This is why the AAOM changed it's By-Laws in 2019 to only allow physicians into it's IROM certification pathway. NDs, DCs, PAs and NPs are no longer allowed in these training programs.

Write to your Law Makers

- What else can we do to ensure safety and preservation of the use of all of the HCT/Ps we have used in our field of Regen Med?
- Write to your congressman and senators requesting that at least BM and Fat fall under 1271.15(b) same day surgical exemption for all MSK indications.
- Consider developing a pathway to get your facility certified as a Class 2 Procedure Center to show you are operating at the safest level.

Shoot for FDA Compliance

- Consider joining a physician group or community that shows effort to attain and remain FDA compliant with these HCT/Ps.
- Renuvi and Regenex may be options to look into.
- Offer your patients to write their state senators and congressman to support 1271.15(b) and specifically to request CEBER put it in writing.

What is Your Risk Tolerance

- Many Physicians will continue to use these HCT/Ps with out any change in their practice.
- This is a choice based on a physician's risk tolerance
- What changed June 1st is the draft guidance language became laws in 2020 and the Homologous Use definition became more clearly defined
- Using Fat and BM is illegal in some ways now

- Letter about fat grafts sent to:
- Bob Casey
- 2000 Market Street
  Suite 610
  Philadelphia, PA 19103
- Pat Toomey
- US Custom House
  200 Chestnut Street
  Suite 600
  Philadelphia, PA 19106
-
- Brian Fitzpatrick
- 1717 Langhorne Newtown Rd. Suite 225
  Langhorne, PA 19047
-
- I am writing to you about the FDA's decision to classify autologous tissue based orthopedic treatments as drugs, and therefore no longer available to people like me.
- My doctor explained to me that the FDA decided on this route because of unscrupulous practitioners in the field.
- Frankly, this is throwing the baby out with the bath water. Fred Upton, a representative from Michigan, has recommended instead a partnership approach to regulating the field of autologous tissue orthopedic treatments. I would urge you to support his efforts to bring a more reasoned approach to these treatments.
- There are tremendous benefits to these treatments, including improved patient health, less invasive procedures, less costly alternatives to surgery, and treatments for conditions that are currently untreatable with standard medical care.
- I'd like to give you some examples of how these treatments have helped me. I have been treated by two different doctors over seven years, and can attest to their expertise and ability to treat chronic orthopedic problems.

June 9, 2021

Sent via Electronic Mail

Peter Marks, M.D., Ph.D.
Director
Center for Biologics Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Ave.
WO71-7232
Silver Spring, MD 20993
peter.marks@fda.hhs.gov

Re: ***FDA Regulation of Autologous Bone Marrow in Orthopedics***

Dear Dr. Marks:

My name is Fred Upton, and I am a member of the U.S. House of Representatives. I serve the people of Michigan's Sixth Congressional District and I am a member of the United States Committee on Energy and Commerce.

I write in reference to FDA's regulation of human cells, tissues, and cellular and tissue-based products ("HCT/Ps"). As I understand the circumstances based on my discussions with the industry and my own independent research, FDA has asserted jurisdiction over HCT/Ps, both autologous and allogeneic, pursuant to its authority under Sections 351 and 361 of the Public Health Service Act (PHSA), as well as its plenary authority under the Food Drug and Cosmetic Act (FDCA). As I also understand, FDA's regulation of HCT/Ps has prevented countless patient injuries at the hands of unscrupulous product manufacturers and practitioners, and the agency's hard work is commendable.

I have recently read that, for roughly 3½ years prior to June 1, 2021, FDA had exercised "enforcement discretion" over much of the HCT/P industry, during which FDA allowed regulated companies to engage in cooperative discussions with the agency without fear of reprisal. From information available online, I have also seen that during that period of enforcement discretion, some HCT/P firms were granted Investigational New Drug (IND) applications, but at the same time FDA continued to enforce against "bad actors" who presented *bona fide* patient safety risks. Now that the period of enforcement discretion has expired, I understand that FDA will more aggressively pursue enforcement actions in an effort to preserve the integrity of America's market of medical products. All of this seems well within reason.

Based on my research, I understand that certain areas of FDA's regulation of the HCT/P industry are clearer than others. For instance, FDA has long since written that the creation of stromal vascular fraction from a patient's fat constitutes the "more than minimal manipulation" of the fat, and

See https://www.fda.gov/news-events/fda-voices/advancing-development-safe-and-effective-regenerative-medicine-products

See e.g. FDA Warning Letter to Liveyon Labs Inc. dated December 6, 2019: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/liveyon-labs-inc-588399-12052019

Historical points in medicine

- *2000 BCE: **Here, eat this root.***
  1000 AD: That root is heathen. Here, say this prayer.
  1850 AD: That prayer is superstition. Here, drink this potion.
  1940 AD: That potion is snake oil. Here, swallow this pill.
  1985 AD: That pill is ineffective. Here, take this antibiotic.
  *2017 AD: That antibiotic is artificial. **Here, eat this root.***

Historical points in orthopedic medicine

- 1950 **Here lets inject with dextrose**
- 1960 It hurts? Lets cut that out.
- 1970: Here take this opiod
- 1980: It hurts? I told you we should have cut that out.
- 1990: Surgery wont work go exercise
- 2000: Lets inject PRP
- 2010: Lets try stem cell injection
- 2015: Stem cell seems to be working lets mix all this together.
- 2019: Stem cell had great promise but we **<u>can not use</u>** that stuff anymore.
- 2020: **Here lets inject with dextrose.**