Orthobiologics Regulation: What You Need to Know
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Any human tissue that’s used outside of what FDA deems as "homologous".
This is the regulation:

- The HCT/P is minimally manipulated; 2) The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer’s objective intent; 3) The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and 4) Either: i) The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or ii) The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and: a) Is for autologous use; b) Is for allogeneic use in a first-degree or second-degree blood relative; or c) Is for reproductive use.
The regulation you need to know is 21 CFR 1271:

- If what you produce in your office crosses the “minimal manipulation” line, then it’s a drug

- There is no protection because you’re a doctor nor because you perform the procedure in a medical setting nor during the same surgical procedure

- There is no protection because you have IRB approval
You can also cross the line by using tissue in a non-homologous way!
Homologous use definition:

- homologous use means 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

- The FDA defines what is homologus for a tissue
  - For Bone Marrow Concentrate, this is only hematopoietic reconstitution
  - For fat grafts it’s only a sub-cutaneous to sub-cutaneous use (that doesn’t not include breast because the FDA’s only recognized function for the breast in lactation)
If you cross the line you will be viewed and inspected as a drug manufacturer...
What does being viewed as a drug manufacturer mean?

- You will need to have a BLA/IND in place (cost 2M USD)
- Just getting your protocol IRB approved means nothing (gets you in more trouble not less)
- You will be held to cGMP
Doesn’t having IRB approval for a study get around all of these regulations?

- NO
- In fact, it just means that you’re now violating both the FDCA and the regulations promulgated by OHRP
What types of orthobiologics are being used today for Orthopedic injuries?
Cord Blood
Isolated from the blood in an umbilical cord of a fetus.

Amniotic Cells taken from the fluid or membrane that surrounds a fetus.

Embryonic Cells taken from the developing embryo.

Synovial Cells isolated from synovial fluid or membrane.

Allogeneic

Bone Marrow Aspirate
Isolated from the liquid part of the bone marrow.

Adipose (Fatty Tissue)
Cells taken from fatty tissue.

Autologous
Autologous
Other than bone marrow, what’s being done in Autologous Therapy?

- Adipose SVF
- Adipose tissue grafts
- IRAP (Regenokine/Orthokine)
Two Different Types of Bone Marrow Stem Cell Processes

Bone Marrow Nucleated Cell Isolation
The stem cell fraction of bone marrow is isolated via a centrifuge and re-injected the same day.

Advanced

Bone Marrow Mesenchymal Stem Cell Culture
The stem cells themselves are isolated and cultured to greater numbers over a few weeks. This produces a “pure” population of stem cells which is different than the mix of cells produced by same day procedures.

Simple Adipose Graft
The fat is separated from the oil and liquid and the fat is injected (however the stem cells are still trapped in the fat and are not concentrated).

Stromal Vascular Fraction (SVF)
The fat is separated and then chemically digested to release the stem cell fraction, which is then concentrated.

Three Different Types of Fat Stem Cell Processes

Simple Adipose Graft
The fat is separated from the oil and liquid and the fat is injected (however the stem cells are still trapped in the fat and are not concentrated).

Stromal Vascular Fraction (SVF)
The fat is separated and then chemically digested to release the stem cell fraction, which is then concentrated.

Adipose Mesenchymal Stem Cell Culture
The stem cells are isolated and cultured to greater numbers over a few weeks. This produces a “pure” population of stem cells which is different than the mix of cells produced by same day procedures.

Tissue Needs FDA Approval

Drug Needs FDA Approval

Tissue No FDA Approval

Drug Needs FDA Approval

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What is SVF?

- A stem cell isolation trend sweeping the country
- “stromal vascular fraction” is a mix of cells that contain MSCs
- It’s created by digesting lipo-aspirate with collagenase or another enzyme
The Fat Stem Cell Mess...

- Fat stem cells, when properly isolated, unlike bone marrow concentrates, are a drug
- This applies even if you’re processing fat at the bedside
- Numerous FDA letters have made this clear
- Some organizations claim this isn’t the case
- Beware, as if you’re caught doing this, you can accused of the production of an illegal drug
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Needs FDA Approval

Tissue
No FDA Approval

One of these is a fat stem cell procedure, the other is not...
In 2012, we obtained lipo-aspirates and then ran these through a mechanical emulsifier:

We got no viable stem cells either through flow cytometry nor through culture.
In 2014, we used a sophisticated vibration assisted lipo-suction machine and then a minimal, regulatory compliant processing:

We got a few viable stem cells via flow cytometry and culture, but much, much less than one would see from a bone marrow concentrate procedure.
Allogeneic
Are Amniotic and Cord “Stem Cell” Products FDA Approved?
New amniotic and cord blood “stem cell” products are springing up monthly.
As discussed before, based on research on these products, they appear to be dead tissue rather than live cellular products.
Many claim that they have a stamp of approval from the FDA.
However, there are two pathways for FDA for donor tissues. The simple 361 registration and the complex and hugely expensive 351 cell drug designation.
All of the amniotic and cord blood products on the market today and being sold for orthopedic uses have a simple 361 registration, which unlike a drug approval, requires no clinical trials or data.
So what’s involved in getting a 361 tissue registration?
This is the actual form that you can submit online.
What happens to one of these companies when it claims there are live cells?

Sec. 1271.10 Are my HCT/P's regulated solely under section 361 of the PHS Act and the regulations in this part, and if so what must I do?

(a) An HCT/P is regulated solely under section 361 of the PHS Act and the regulations in this part if it meets all of the following criteria:

(1) The HCT/P is minimally manipulated;

(2) The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent;

(3) The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and

(4) Either:

(i) The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or

(ii) The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and:

(a) Is for autologous use;

(b) Is for allogeneic use in a first-degree or second-degree blood relative; or

(c) Is for reproductive use.

(b) If you are a domestic or foreign establishment that manufactures an HCT/P described in paragraph (a) of this section:

(1) You must register with FDA;

(2) You must submit to FDA a list of each HCT/P manufactured; and

(3) You must comply with the other requirements contained in this part.
It’s a 351 cell drug that must go through hundreds of millions of dollars and 5-10 years of clinical trials.
Do you Have Legal Liability as the Physician who Uses an Illegal Biologic Drug?
There are two regenerative medicine products right now that are misbranded and adulterated (illegal) drugs...
These are:

• Amniotic or cord products which claim that they have live cells
• Culture expanded bone marrow or fat
Some claim that they are using these products as part of an IRB approved study, but to do that requires a separate multi-million dollar biologics license from the FDA for each medical indication.
But how could you get in trouble for just receiving these illegal drugs? After all, the real legal liability is on the manufacturer, right?
You are legally liable:

- At section 301, the FDCA states what is illegal:

  "The receipt in interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded, and the delivery or proffered delivery thereof for pay or otherwise"[FD&C Act, sec. 301(c); 21 U.S.C. 331(c)].

https://www.fda.gov/cosmetics/guidanceregulation/lawsregulations/ucm074248.htm
Scenario 1:

- You order and pay for an amniotic or cord blood product that because it claims that it has live cells in an email, is an adulterated and misbranded drug product.

- Why? This product pursued a simple online 361 registration. However FDA requires all living allogeneic cell products to pursue FDA approval with clinical trials as a 351 drug product.
Scenario 2:

- You send bone marrow or fat to be cultured at a manufacturer’s site as part of what you are told is an “IRB approved” study and pay for and inject the expanded cells in a patient. This is an adulterated and misbranded drug product. Why?

- Studying a cultured cell product in the US requires a separate FDA BLA to be place for every clinical indication. The company didn’t pursue this type of permission but only got an IRB approval from a group that didn’t have the proper credentials to oversee an FDA drug study.
Don’t end up in federal prison or defending yourself from federal indictment because you believed a sales rep. Do your own homework...
If a company claims to be selling live cells, ask to see their FDA drug approval documents (not their simple 361 online tissue registration). They should have years of extensive clinical trials data to show you.
If a company wants to culture your patients stem cells, they will need to show you a separate biologics license application approval for each clinical indication.
How do we prevent orthopedic BMC and fat grafts from falling into the regulatory abyss?
The 4 Ps:

- **Partition**: separate orthobiologics from the miracle cure stem cell clinics.
- **PR**: Educating the world about the benefits of orthobiologics.
- **Pressure**: Patients and stakeholders need to organize to bring pressure to bear on legislators.
- **Publish**: Review articles need to be placed in key publications that scientifically demonstrate the ways that orthobiologics are homologous to the MSK system.