FDA Regulation of Adipose Stem Cell Therapies: Separating Fat from Fiction

Mary Ann Chirba, Professor, Boston College Law School

Public Perception and Policy Development in Consent Standards for Human Research—How Competing Views on Public Goods and Private Interests Shape Data Sharing, Big Data Research, and Other Activities Using Human Data and Materials”

Valerie Bonham, Counsel, Ropes & Gray LLP

Discussant: **Kalah Auchincloss**, Senior Vice President, Regulatory Compliance & Deputy General Counsel, Greenleaf Health, LLC
Moderator: **Barbara Binzak Blumenfeld**, Shareholder, Buchanan Ingersoll & Rooney PC

FDLI

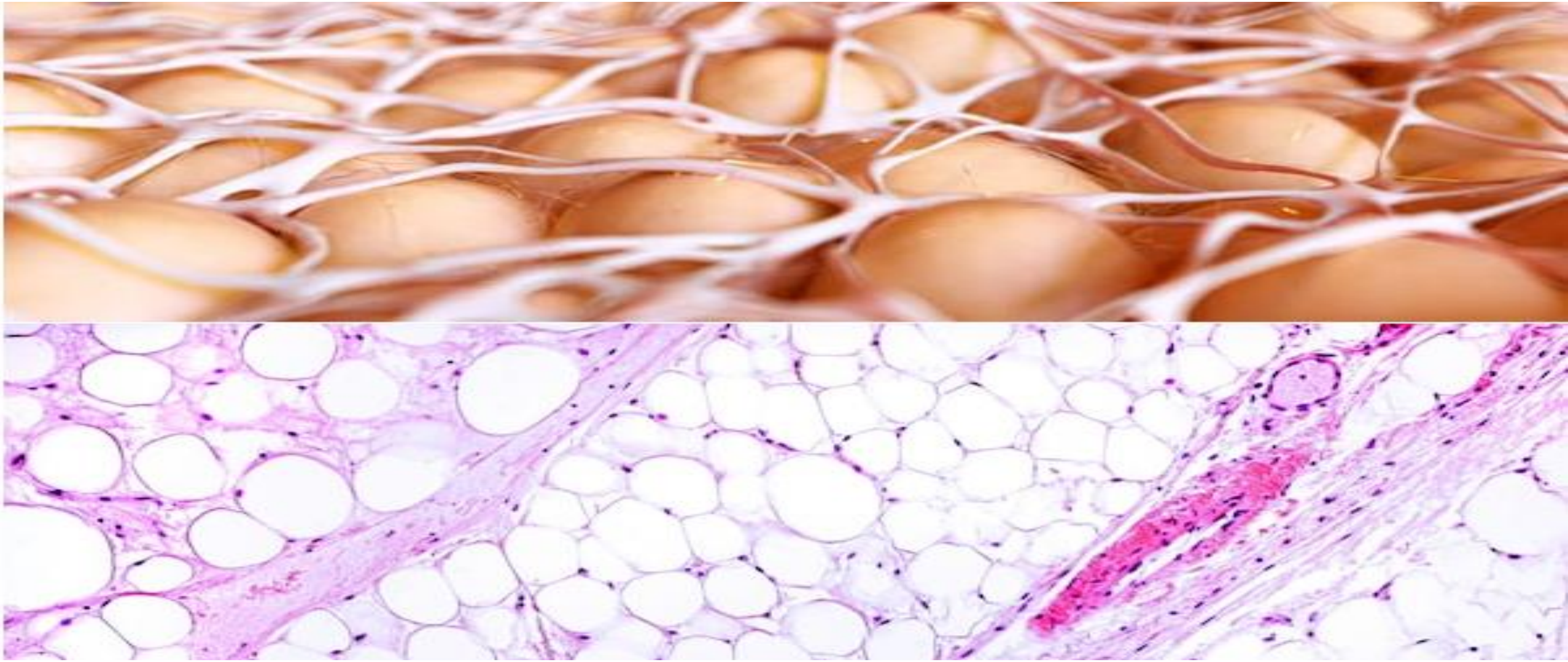
FDA Regulation
of
Adipose Stem Cell Therapies:
Separating Fat from Fiction

MARY ANN CHIRBA, J.D., D.SC., M.P.H.
BOSTON COLLEGE LAW SCHOOL

November 2019

FDLI

2019



U.S. FOOD & DRUG ADMINISTRATION

UPS EXPRESS MAIL

[May 2019]

Based on a review of your website, it appears that [redacted] does not qualify for any exception in 21 CFR 1271.15 and the stem cell therapies offered by [redacted] are **intended for nonhomologous uses** and would be regulated as drugs as defined in section 201(g) of the FD&C Act [21 U.S.C. 321(g)] and biological products as defined in section 351(i) of the PHS Act [42 U.S.C. 262(i)]. In order to lawfully market a drug that is also a biological product, **a valid biologics license must be in effect** [42 U.S.C. 262(a)]. Such licenses are **issued only after a demonstration that the product is safe, pure, and potent.** While in the development stage, such products **may be distributed for clinical use in humans only if the sponsor has an investigational new drug (IND) application in effect** as specified by FDA regulations [21 U.S.C. 355(i); 42 U.S.C. 262(a)(3); 21 CFR Part 312].

U.S. FOOD & DRUG ADMINISTRATION

UPS EXPRESS MAIL

[May 2019]

We note that your products are intended to treat a variety of serious or life-threatening diseases or conditions. **Such unapproved uses raise potential significant safety concerns.** Additionally, because the products are **administered by various higher risk routes of administration, including IV, their use, if contaminated could cause a range of adverse events.** …

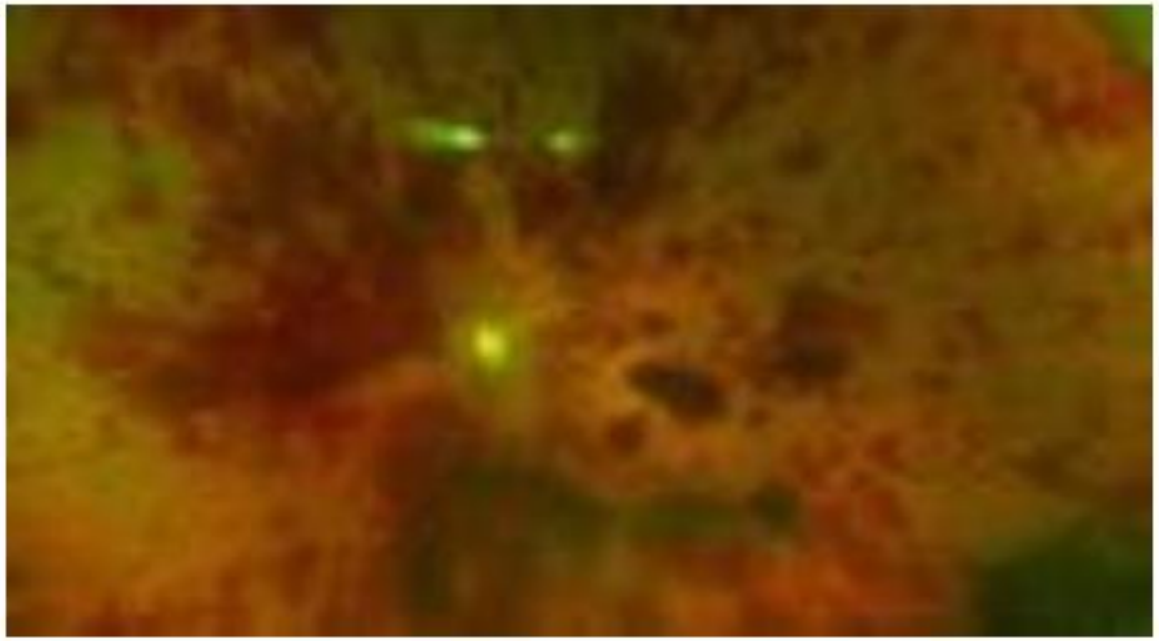
… **You and your firm are responsible for ensuring that all your products fully comply with the PHS and FD&C Acts and all applicable regulations.**

May 2019: "Based on a review of your website, it appears that…"

June 2019:

Health

FDA wins groundbreaking case against for-profit stem cell company



A picture of a patient's eye one week after receiving stem cell injections from U.S. Stem Cell in 2015 shows widespread retinal hemorrhages. (Thomas Albini/, MD)

By **William Wan** and **Laurie McGinley**

June 4, 2019 at 11:50 AM EDT

In a decision expected to SEND A CHILL through the booming STEM CELL INDUSTRY, *a federal judge RULED IN FAVOR OF THE FDA* on Monday in a lawsuit against a Florida-based stem cell company whose treatments have blinded at least four patients.

May 2019: "Based on a review of your website, it appears…"
June 2019: Court win will "SEND A CHILL"
Nov. 2019: How did that 1st website respond?

"Consumer Guide to Amniotic & Umbilical Cord SC Therapy"

"Debunk myths" → Consumers can make an "educated decision"

"Are there any ethical issues with these biologics?

No there are not.

Any ethical issues? "NO THERE ARE NOT."

"In the research literature and from our provider's experience, **BENEFITS ARE BEING SHOWN:**

- **Neurologic Conditions:**
- **Heart/Kidney/Lung Failure (e.g. Cardiomyopathy, COPD) …**
- **Cerebral Palsy …**
- **Diabetes …**

WORKS WELL OVERALL for …

NEURODEGENERATIVE ISSUES, AUTISM, STROKE, ORGAN FAILURE, AUTOIMMUNE CONDITIONS & "tough to treat" issues like **Lyme disease.**

"Why are regenerative procedures with [AMNIOTIC & UMBILICAL] products so popular?"

1. **No harvest**
2. **Safe**
3. **Consistent**
4. **Excellent outcomes**

"There are too many studies to count looking at the effectiveness of amniotic/umbilical tissue to treat musculoskeletal conditions."

"When you look at the very high Benefit profile and the very low Risk profile of these materials, in medicine that is called

A HOME RUN!"

“What are the Risks of Amniotic and Umbilical Tissue?”

- **Overall, the risk profile of these materials is exceptionally low.** They do not contain steroid, so there is no worry of adrenal gland or blood sugar issues.

- **Standard procedure risks exist that include infection, bleeding, nerve injury, allergic reaction.** As an example, many providers will use contrast to ensure accurate needle placement. Once in a blue moon, this contrast material may spark an allergic reaction.

- **Additional risks may include disease transmission or rejection reaction.** As mentioned earlier, **the FDA certified lab** goes through considerable processing to remove ANY DNA factors that could cause this reaction. In addition, **the FDA has very strict regulations on how the tissue is tested** for many, many diseases. **After thousands of cases, R3’s affiliated providers have never seen either of these issues but it needs to be mentioned.**

- **The biggest risk** actually with any regenerative procedure, whether performed with bone marrow, adipose, amniotic or umbilical tissue, **is that it may not work.** While that is a sub-optimal outcome obviously, no bridge has been burned. With a joint replacement, there is no going back. Same with an organ transplant!

"Are these procedures FDA Approved?"

- **"No they are not. … they fall into the biologics category…**
- **These are regulated heavily by the FDA, but do not get approved or denied."**

Here is how the FDA regulates things:

- **Biologics – the FDA strictly regulates how biologic materials are acquired, processed, stored and used under the CFR Part 1271.**

- **Amniotic and umbilical materials fall under this category, which does not involve an Approval/Denial process like drugs do.**

  - **Specifically, the section under Part 1271 that applies to amniotic/umbilical tissues is Section 361 products, which are not required to be licensed or approved by the FDA and are regulated under Section 361 of the Public Health Service (PHS) Act.**

But remember?

UPS EXPRESS MAIL

[May 2019]

Based on a review of your website, it appears that [redacted] does not qualify for any exception in 21 CFR 1271.15 and the stem cell therapies offered by [redacted] are **intended for nonhomologous uses** and would be regulated as drugs as defined in section 201(g) of the FD&C Act [21 U.S.C. 321(g)] and biological products as defined in section 351(i) of the PHS Act [42 U.S.C. 262(i)]. In order to lawfully market a drug that is also a biological product, **a valid biologics license must be in effect** [42 U.S.C. 262(a)]. Such licenses are **issued only after a demonstration that the product is safe, pure, and potent.** While in the development stage, such products **may be distributed for clinical use in humans only if the sponsor has an investigational new drug (IND) application in effect** as specified by FDA regulations [21 U.S.C. 355(i); 42 U.S.C. 262(a)(3); 21 CFR Part 312].

Nov. 2019: “Where can I find a reputable provider for these procedures?”

“[ ] nationwide where you can obtain regenerative procedures. **If the center closest to you does not perform the necessary procedure (e.g. for DEMENTIA OR AUTISM),** we have a concierge service to assist your travel needs to one that does!”

…….

But remember?

“Are there any ethical issues with these biologics?

No there are not.”

WHITE-OAK

WE HAVE A PROBLEM

“What we’re playing now is a game of Whack-a-Mole.”

Peter Marks, Dir. CBER - “Bad Batch” podcast, Nov. 13, 2019

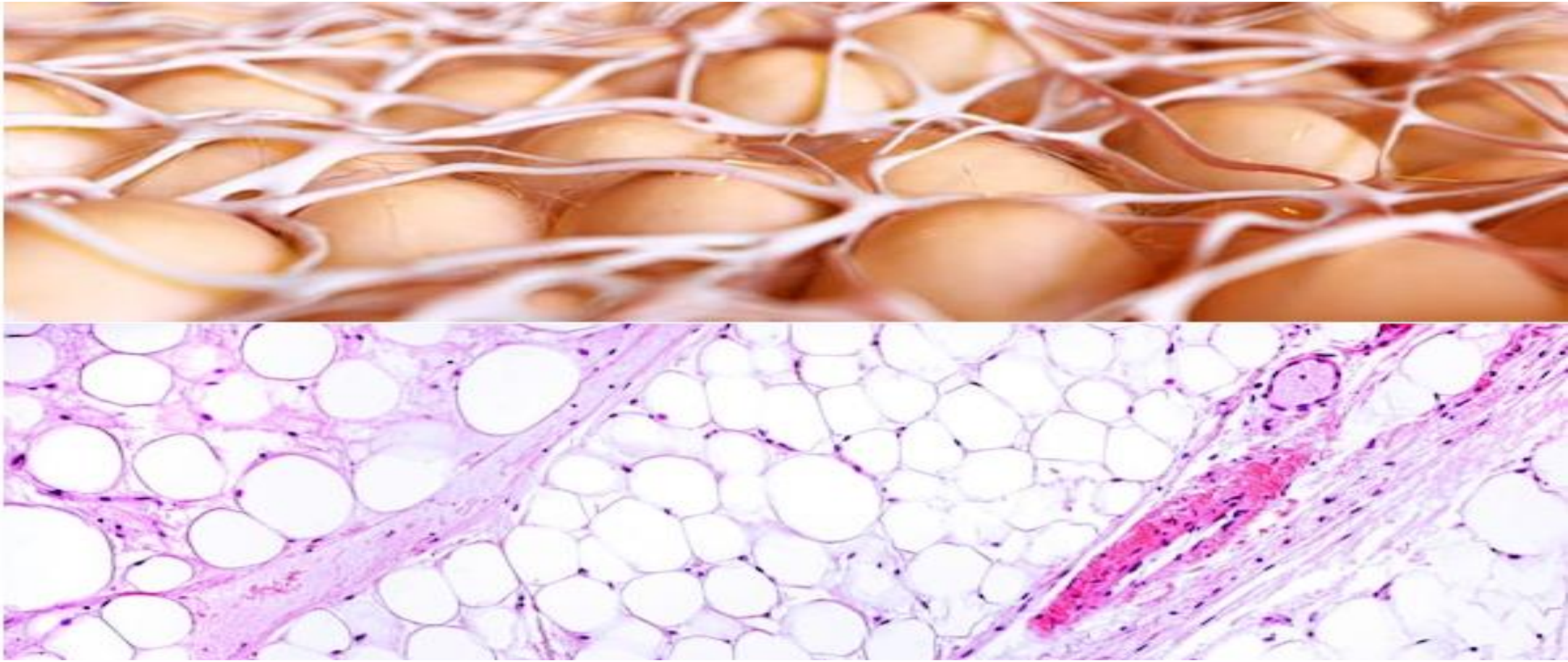
“We’ve got major issue here, and WE HAVE TO TRIAGE....”

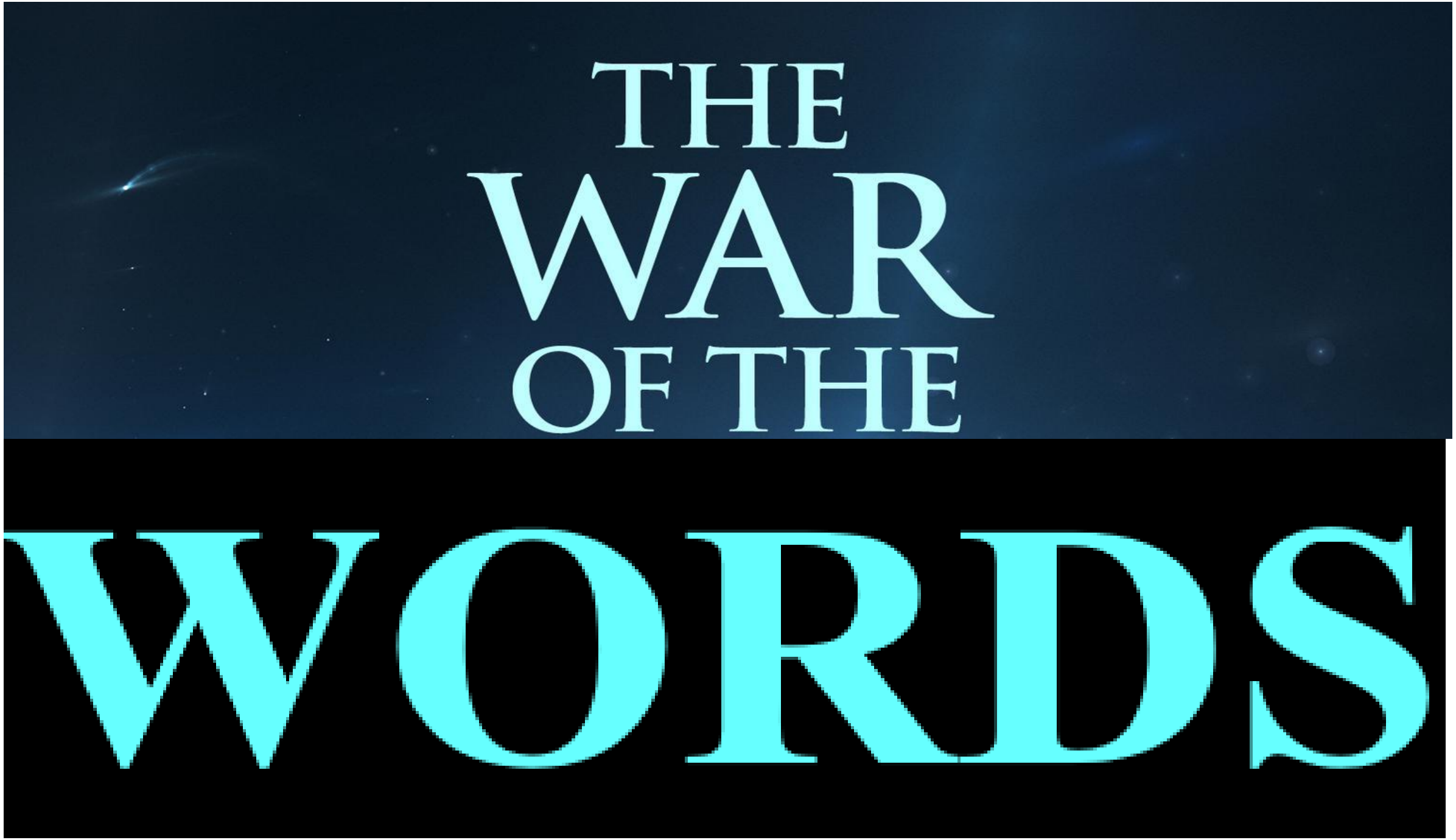
Peter Marks, “Bad Batch” podcast Nov.. 13, 2019

- **We just want to see that they’re safe & effective**
- **Incredibly hard to keep track of…**
- **They keep changing their products…**
- **Trying to keep track of the clinics is nearly impossible because**
- **Entities that come and go very quickly.**
- **We would like to take more enforcement actions but**
- **SLOW and deliberate because have to work through process of law.**

How did we get here?

Regulation




THE
WAR
OF THE
WORDS

The Battle to AVOID § 351 PREMARKET APPROVAL

§ 351 Same Surgical Procedure Exception

a) **AUTOLOGOUS**

a) Implant in **SAME SURGICAL PROCEDURE**

a) Remain "such HCT/Ps" in **ORIGINAL FORM**

§ 361 HCT/P

1. **MINIMALLY MANIPULATED**
2. **HOMOLOGOUS USE**
3. **No combo w/ another article"**
4. **PRIMARY FUNCTION:**

   NOT SYSTEMIC or METABOLIC

   OR

   SYSTEMIC + METABOLIC

   AND

   AUTOLOGOUS

   Allogeneic 1st or 2nd degree blood Reproductive use

Minimal Manipulation

21 CFR 1271.3(f)

STRUCTURAL **tissue**: processing **does not alter**
original ***RELEVANT*** **characteristics** re: tissue's
utility for reconstruction, repair, or replacement

CELLS or NON-STRUCTURAL **tissues**: processing **does not alter**
RELEVANT biological characteristics of cells or tissues.

HOMOLOGOUS USE

21 CFR 1271.3(c)

- ***Same basic function or functionS*** in ***Donor & Recipient based on Mfr's INTENDED USE***

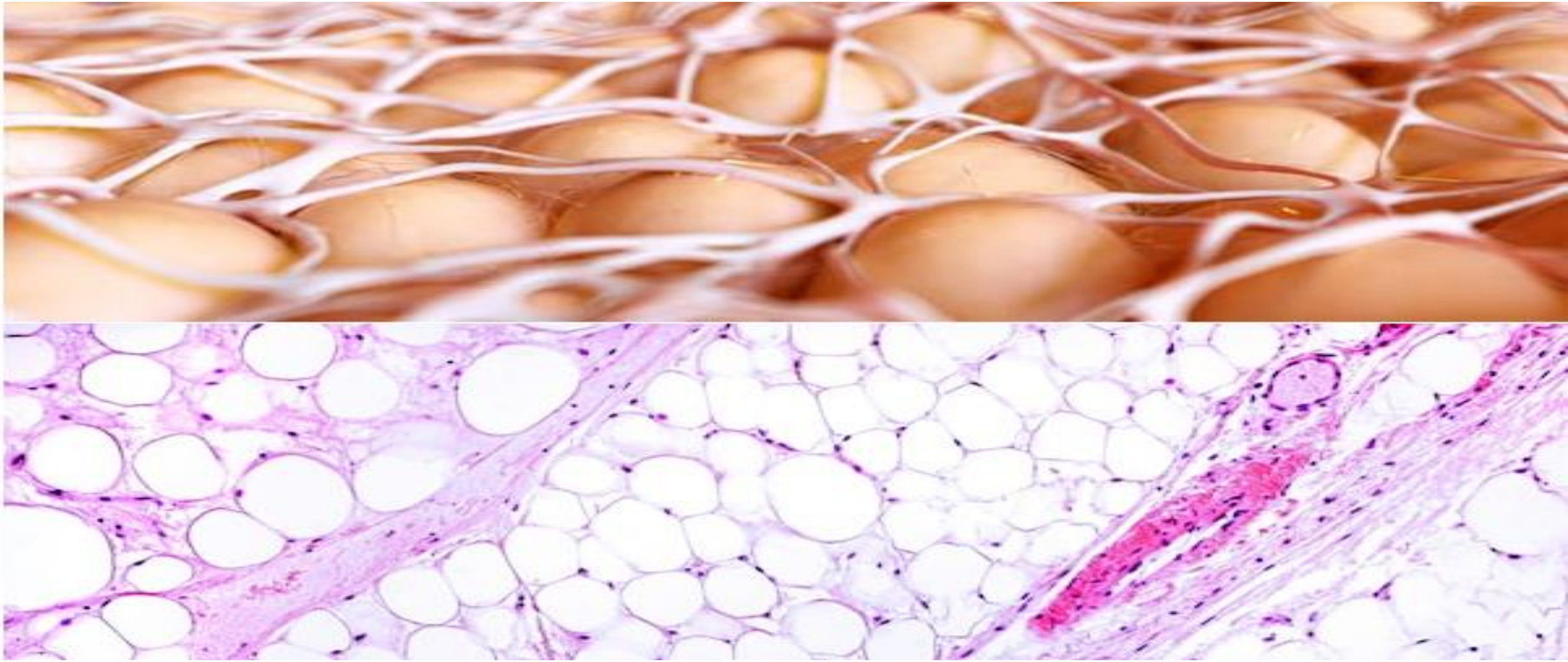
- ***What HCTP does in Donor or is CAPABLE of doing when in its original/native state***
  - **Need not perform all basic functions**
  - **Need not perform in same location**

- **Structural: structural function in recipient**
  - **physically support**, barrier, conduit, **connective**, cover, or cushion

.

- **Cellular / Nonstructural: METABOLIC or biochemical function in recipient**
  - hematopoietic, immune, and **ENDOCRINE** functions.

Interpretation 2014-2016



FDA's 4 DRAFT HCTP Guidances

10.23.14 Same Surgical Procedure Exception
12.23.14 Minimal Manipulation
12.24.14 Adipose-derived HCT/Ps
10.30.15 Homologous Use

……

FDA GOAL: ***↑ Stakeholders' understanding + ↓ RISK***

Results: ***↑ Ambiguities & inaccuracies =***
↓ Stakeholders' understanding = ↑ RISK

……

04.2016 ***Unanticipated response; Comment period extended 2x***
09.13.15 ***2 day Public Meeting + Worlshop***
09. 27.16 ***Final comments due***

Draft Guidances Criticized for Treatment of Adipose

1) Adipose PREDOMINANTLY NONSTRUCTURAL / Metabolic / Endocrine

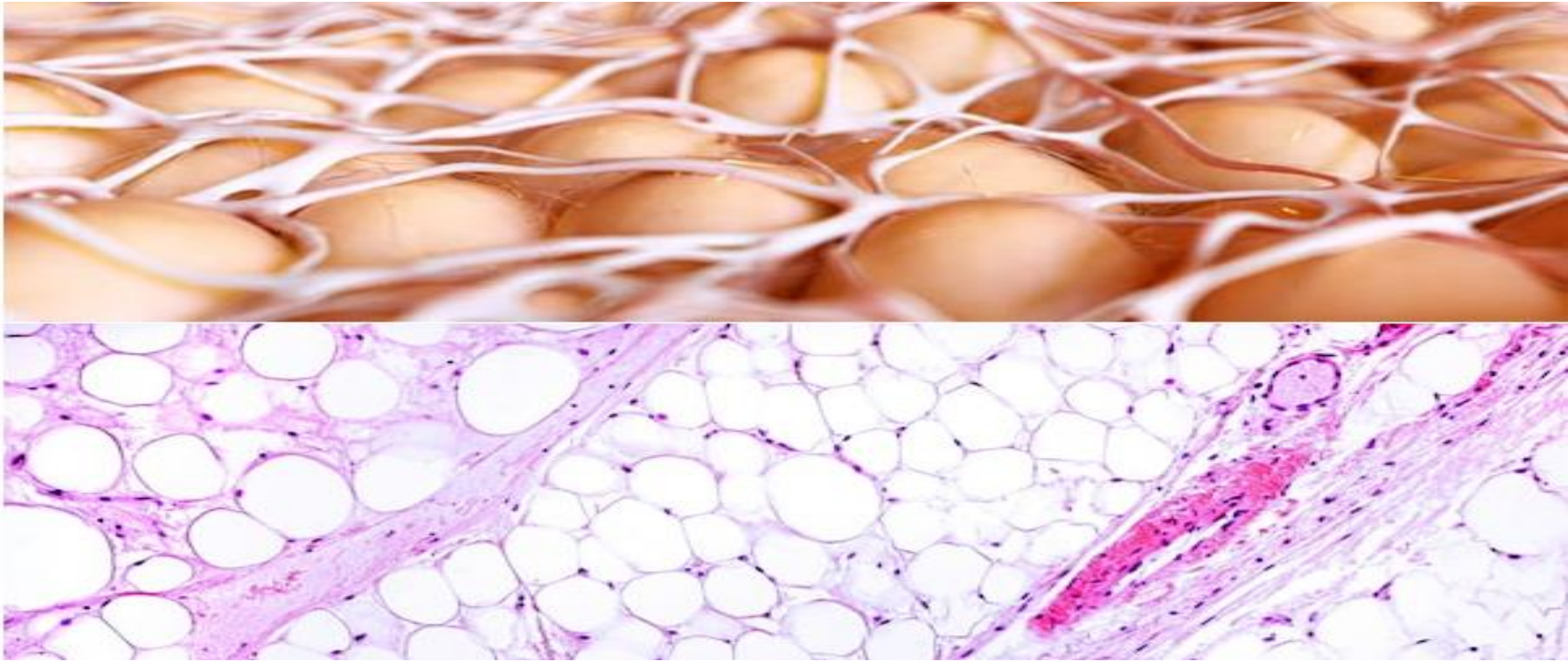
2) Adipose for Breast Reconstruction → Structural

- ***Homologous, right?***
- ***Wrong!***

- **"The BASIC FUNCTION of breast tissue is to produce milk (lactation) after childbirth. Because this is not a basic function of adipose tissue" → Non-Homologous**

- **Breast Reconstruction: Autograft Flap procedures**
  - **All use vascularized tissue**
  - **All involve adipose tissue**
  - **Implant w/ Adipose (padding, cushioning, shape)**

Interpretation 2017



Nov. 16, 2017 … FDA Implements Cures Act:
"COMPREHENSIVE" Regen. Med. Framework

Scott Gottlieb:

- Regenerative medicine **"no longer the stuff of science fiction"**
- **"One of the most promising fields of science"**
- **"Transformative promise for patients"**

BUT …

- **"Rapid growth**, dynamism and complexity means …
- **"UNIQUE CHALLENGES** to researchers, health care providers & FDA

GOALS

- **PATIENT SAFETY & Support INNOVATION**
- **Risk-based** scientific framework & **Least burdensome, Flexible**

Strategies

- **Innovative trial designs** to support FDA approval
- **36 mos. Enforcement Discretion - allow FDA consults** re: need for PMA, what to submit

- **ENFORCEMENT PRIORITY: Target unscrupulous**, **Jeopardize patient safety &** progress of field

FDA Nov. 2017 Comprehensive RMT Framework: 4 Guidance Docs

2 FINAL ⇨ 4 Pre- Cures / 2014-2015 draft guidances merged

§ 351 SSP Exception (+ Adipose)

Min. Manip & Homologous Use (+ Adipose)

2 FINAL ⇨ Implement Cures Act

RMAT Designation to Expedite

RMT Devices

Clarifying "Basic Function or functionS"

Final MM/HU Guidance, Nov. 2017:

"BASIC FUNCTIONS ARE WELL UNDERSTOOD"

"It should not be necessary

to perform laboratory, pre-clinical, or clinical studies

to demonstrate a basic function or FUNCTIONS…."

Same Definitions of STRUCTURAL v. NONSTRUCTURAL

REGULATION creates 2 categories based on FUNCTION: *Binding!*

1. **STRUCTURAL**: **Processing does not alter original RELEVANT characteristics re:**
   utility for RECONSTRUCTION, REPAIR, OR REPLACEMENT

2. **NONSTRUCTURAL: Processing does not alter original RELEVANT biological characteristics** of cells or tissues w/ **PREDOMINANTLY METABOLIC or BIOCHEMICAL** such as **hematopoietic, immune, ENDOCRINE, etc.**

……

CORRECTS Breast, Lactation → Adipose for Structural Support in Breast Reconstruction

→ Homologous

<u>The PROBLEM</u>: NOT the definitions/categories, but their APPLICATION to ADIPOSE

FDA insists ONLY 1 category & USING THE WRONG ONE → STRUCTURAL

ADIPOSE → padding, cushioning, protects vs. shocks; stores fat → Okay for Breast Reconstr

<u>BIOLOGY</u>: Adipose predominantly METABOLIC/biochemical → ENDOCRINE → NONSTRUCTURAL

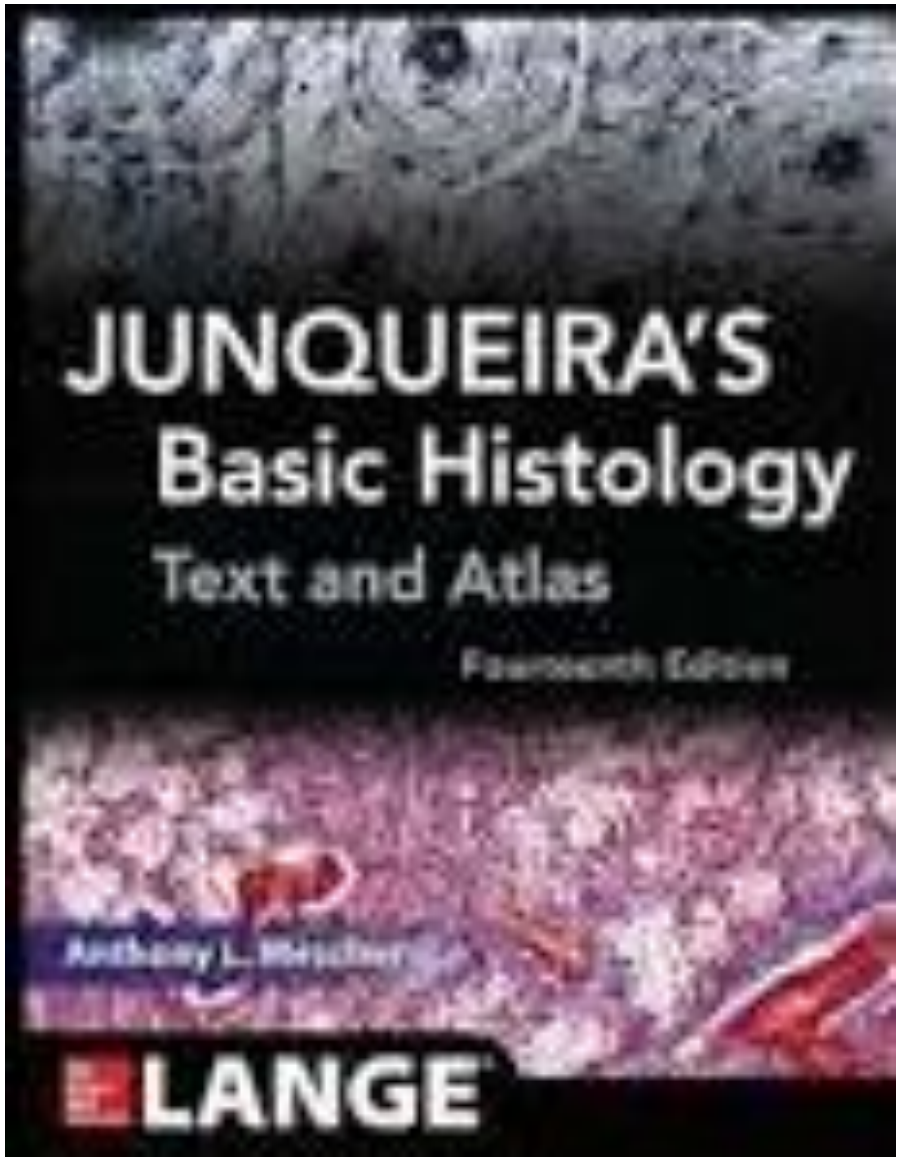
2017 FDA is Wrong: ⇨ It evaluates Adipose as SOLELY Structural but it's Actually NONSTRUCTURAL

B.6. Structural Tissue: What types of tissues are considered structural tissues?

- Physically **support, barrier or conduit, connect, cover, or cushion *in DONOR***
- **Adipose tissue is typically defined as a connective tissue composed** of clusters of cells (adipocytes) surrounded by a reticular fiber network and interspersed small blood vessels, divided into lobes and lobules by connective tissue septa.
- **While adipose tissue has *multiple functions*,**
- it is ***predominantly composed of adipocytes and surrounding connective tissues that provide cushioning and support to the body***
- ***"FDA considers adipose tissue to be a structural tissue***

for the purpose of applying the HCT/P regulatory framework."

FDA cites as support:
Junqueira's Histology Text on Adipose:



- ***FDA's cites 13th Ed. 2013: Does not support***
- ***Outdated 14th Ed: 2015 – Chapter 6:***
- ***Sentence # 4: "Adipocytes function as***

  KEY REGULATORS of overall energy METABOLISM."
- ***Sentence # 11: "Adipose tissue is NOW RECOGNIZED AS AN IMPORTANT ENDOCRINE TISSUE."***
- ***Sentence # 14:*** Adipose tissue ***ALSO fills up spaces*** between other tissues and ***helps cushion*** and keep some organs in place.
- ***Also cites 2010 article: Authors since published on NONSTRUCTURAL uses***

FDA 2 cites: Adipose SOLELY Structural v. Adipose also NONstructural

REFERENCES

1. Bourin P, Bunnell BA, Casteilla L, Dominici M, Katz AJ, March KL, Redl H, Rubin JP, Yoshimura K, Gimble JM. Stromal cells from the adipose tissue-derived stromal vascular fraction and culture expanded adipose tissue-derived stromal/stem cells: A joint statement of the International Federation for Adipose Therapeutics and Science (IFATS) and the International Society for Cellular Therapy (ISCT). *Cytotherapy*. 2013;15:641-648
2. Diaz-Flores L, Gutierrez R, Madrid JF, Varela H, Valladares F, Acosta E, Martin-Vasallo P, Diaz-Flores L, Jr. Pericytes. Morphofunction, interactions and pathology in a quiescent and activated mesenchymal cell niche. *Histol Histopathol*. 2009;24:909-969
3. Gimble JM. The function of adipocytes in the bone marrow stroma. *The New Biologist*. 1990;2:304-312
4. Cawthorn WP, Scheller EL, Learman BS, Parlee SD, Simon BR, Mori H, Ning X, Bree AJ, Schell B, Broome DT. Bone marrow adipose tissue is an endocrine organ that contributes to increased circulating adiponectin during caloric restriction. *Cell metabolism*. 2014;20:368-375
5. Meunier P, Aaron J, Edouard C, VlGNON G. Osteoporosis and the replacement of cell populations of the marrow by adipose tissue: A quantitative study of 84 iliac bone biopsies. *Clinical orthopaedics and related research*. 1971;80:147-154
6. G. N. Über die wiederanheilung vollstädig vom körper getrennter, die ganze fettschicht en- thaltender hautstucke. *Zbl f Chir* 1893;30:16-17
7. Hollander E, Joseph M. Cosmetic surgery. *Handbuch der Kosmetik. Leipzig, Germany: Veriag von Velt*. 1912;688
8. Miller CC. *Cannula implants and review of implantation technics in esthetic surgery: In two parts*. Oak Press; 1926.
9. Gimble JM FZ. Fat circadian biology. *Journal of applied physiology.* 2009;107:1629-1637
10. Tartaglia LA, Dembski M, Weng X, Deng N, Culpepper J, Devos R, Richards GJ, Campfield LA, Clark FT, Deeds J. Identification and expression cloning of a leptin receptor, ob-r. *Cell*. 1995;83:1263-1271
11. Salgado AJ, Gimble JM. Secretome of mesenchymal stem/stromal cells in regenerative medicine. *Biochimie*. 2013;95:2195
12. Salgado AJ, Reis RL, Sousa N, Gimble JM. Adipose tissue derived stem cells secretome: Soluble factors and their roles in regenerative medicine. *Curr Stem Cell Res Ther*. 2009
13. Khan M, Joseph F. Adipose tissue and adipokines: The association with and application of adipokines in obesity. *Scientifica*. 2014;2014
14. Vicennati V, Garelli S, Rinaldi E, Di Dalmazi G, Pagotto U, Pasquali R. Cross-talk between adipose tissue and the hpa axis in obesity and overt hypercortisolemic states. *Hormone molecular biology and clinical investigation*. 2014; 17:63-77
15. Kargi AY, Iacobellis G. Adipose tissue and adrenal glands: Novel pathophysiological mechanisms and clinical applications. *International journal of endocrinology*. 2014;2014
16. Maïmoun L, Georgopoulos NA, Sultan C. Endocrine disorders in adolescent and young female athletes: Impact on growth, menstrual cycles, and bone mass acquisition. *The Journal of Clinical Endocrinology & Metabolism*. 2014;99:4037-4050
17. McIntosh K, Zvonic S, Garrett S, Mitchell JB, Floyd ZE, Hammill L, Kloster A, Di Halvorsen Y, Ting JP, Storms RW. The immunogenicity of human adipose-derived cells: Temporal changes in vitro. *Stem cells*. 2006;24:1246-1253
18. McIntosh KR, Frazier T, Rowan BG, Gimble JM. Evolution and future prospects of adipose-derived immunomodulatory cell therapeutics. *Expert review of clinical immunology*. 2013;9:175-184
19. McIntosh KR, Lopez MJ, Borneman JN, Spencer ND, Anderson PA, Gimble JM. Immunogenicity of allogeneic adipose-derived stem cells in a rat spinal fusion model. *Tissue Engineering Part A*. 2009;15:2677-2686
20. Mitchell JB, McIntosh K, Zvonic S, Garrett S, Floyd ZE, Kloster A, Di Halvorsen Y, Storms RW, Goh B, Kilroy G. Immunophenotype of human adipose-derived cells: Temporal changes in stromal-associated and stem cell–associated markers. *Stem cells*. 2006; 24:376-385
21. Gimble JM, Dorheim MA, Cheng Q, Medina K, Wang CS, Jones R, Koren E, Pietrangeli C, Kincade PW. Adipogenesis in a murine bone marrow stromal cell line capable of supporting b lineage lymphocyte growth and proliferation: Biochemical and molecular characterization. *European journal of immunology*. 1990;20:379-387
22. Frazier TP, McLachlan JB, Gimble JM, Tucker HA, Rowan BG. Human adipose-derived stromal/stem cells induce functional cd4+ cd25+ foxp3+ cd127− regulatory t cells under low oxygen culture conditions. *Stem cells and development*. 2014;23:968-977
23. Frazier TP, Gimble JM, Kheterpal I, Rowan BG. Impact of low oxygen on the secretome of human adipose-derived stromal/stem cell primary cultures. *Biochimie*. 2013;95:2286-2296
24. Miranville A, Heeschen C, Sengenes C, Curat C, Busse R, Bouloumie A. Improvement of postnatal neovascularization by human adipose tissue-derived stem cells. *Circulation*. 2004;110:349-355
25. Rehman J, Traktuev D, Li J, Merfeld-Clauss S, Temm-Grove CJ, Bovenkerk JE, Pell CL, Johnstone BH, Considine RV, March KL. Secretion of angiogenic and antiapoptotic factors by human adipose stromal cells. *Circulation*. 2004;109:1292-1298
26. Planat-Benard V, Silvestre J-S, Cousin B, André M, Nibbelink M, Tamarat R, Clergue M, Manneville C, Saillan-Barreau C, Duriez M. Plasticity of human adipose lineage cells toward endothelial cells physiological and therapeutic perspectives. *Circulation*. 2004;109:656-663
27. Kilroy GE, Foster SJ, Wu X, Ruiz J, Sherwood S, Heifetz A, Ludlow JW, Stricker DM, Potiny S, Green P, Halvorsen YD, Cheatham B, Storms RW, Gimble JM. Cytokine profile of human adipose-derived stem cells: Expression of angiogenic, hematopoietic, and pro- inflammatory factors. *J Cell Physiol*. 2007;212:702-709
28. Ribeiro CA, Fraga JS, Grãos M, Neves NM, Reis RL, Gimble JM, Sousa N, Salgado AJ. The secretome of stem cells isolated from the adipose tissue and wharton jelly acts differently on central nervous system derived cell populations. *Stem Cell Res Ther*. 2012;3:18
29. Silva NA, Gimble JM, Sousa N, Reis RL, Salgado AJ. Combining adult stem cells and olfactory ensheathing cells: The secretome effect. *Stem cells and development*. 2013;22:1232-1240
30. Cho YJ, Song HS, Bhang S, Lee S, Kang BG, Lee JC, An J, Cha CI, Nam DH, Kim BS. Therapeutic effects of human adipose stem cell-conditioned medium on stroke. *Journal of neuroscience research*. 2012;90:1794-1802

References

31. Egashira Y, Sugitani S, Suzuki Y, Mishiro K, Tsuruma K, Shimazawa M, Yoshimura S, Iwama T, Hara H. The conditioned medium of murine and human adipose-derived stem cells exerts neuroprotective effects against experimental stroke model. *Brain research*. 2012;1461:87-95

32. Wei X, Du Z, Zhao L, Feng D, Wei G, He Y, Tan J, Lee WH, Hampel H, Dodel R. Ifats collection: The conditioned media of adipose stromal cells protect against hypoxia-ischemia-induced brain damage in neonatal rats. *Stem Cells*. 2009;27:478-488

33. Wei X, Zhao L, Zhong J, Gu H, Feng D, Johnstone B, March K, Farlow M, Du Y. Adipose

stromal cells-secreted neuroprotective media against neuronal apoptosis. *Neuroscience letters*. 2009;462:76-79

34. Zhao L, Wei X, Ma Z, Feng D, Tu P, Johnstone B, March K, Du Y. Adipose stromal cells-conditional medium protected glutamate-induced cgns neuronal death by bdnf. *Neuroscience letters*. 2009;452:238-240

35. Cousin B, André M, Arnaud E, Pénicaud L, Casteilla L. Reconstitution of lethally irradiated mice by cells isolated from adipose tissue. *Biochemical and biophysical research communications*. 2003;301:1016-1022

36. Han J, Koh YJ, Moon HR, Ryoo HG, Cho CH, Kim I, Koh GY. Adipose tissue is an extramedullary reservoir for functional hematopoietic stem and progenitor cells. *Blood*.2009

37. Harms M, Seale P. Brown and beige fat: Development, function and therapeutic potential. *Nature medicine*. 2013;19:1252-1263

38. Rahman S, Lu Y, Czernik PJ, Rosen CJ, Enerback S, Lecka-Czernik B. Inducible brown adipose tissue, or beige fat, is anabolic for the skeleton. *Endocrinology*. 2013;154:2687-2701

39. Wu J, Cohen P, Spiegelman BM. Adaptive thermogenesis in adipocytes: Is beige the new brown? *Genes & development*. 2013;27:234-250

40. Krings A, Rahman S, Huang S, Lu Y, Czernik P, Lecka-Czernik B. Bone marrow fat has brown adipose tissue characteristics, which are attenuated with aging and diabetes. *Bone*. 2012;50:546-552

41. van Marken Lichtenbelt WD, Vanhommerig JW, Smulders NM, Drossaerts JM, Kemerink GJ, Bouvy ND, Schrauwen P, Teule GJ. Cold-activated brown adipose tissue in healthy men. *N Engl J Med*. 2009;360:1500-1508

42. Peirce V, Carobbio S, Vidal-Puig A. The different shades of fat. *Nature*. 2014;510:76-83

43. Enerbäck S, Gimble JM. Lipoprotein lipase gene expression: Physiological regulators at the transcriptional and post-transcriptional level. *Biochimica et Biophysica Acta (BBA)- Lipids and Lipid Metabolism*. 1993;1169:107-125

44. Rudolph MC, Neville MC, Anderson SM. Lipid synthesis in lactation: Diet and the fatty acid switch. *Journal of mammary gland biology and neoplasia*. 2007;12:269-281

45. Gimble JM, Katz AJ, Bunnell BA. Adipose-derived stem cells for regenerative medicine. *Circ Res*. 2007;100:1249-1260

46. Bellows CF, Zhang Y, Chen J, Frazier ML, Kolonin MG. Circulation of progenitor cells in obese and lean colorectal cancer patients. *Cancer Epidemiology Biomarkers & Prevention*. 2011;20:2461-2468

47. Bellows CF, Zhang Y, Simmons PJ, Khalsa AS, Kolonin MG. Influence of bmi on level of circulating progenitor cells. *Obesity*. 2011;19:1722-1726

48. Krijnen PA NB, Meinster E, Vo K, Musters RJ, Kamp O, Niessen HW,, Juffermans LJ VDA.

Acute myocardial infarction does not affect functional characteristics of adipose derived stem cells in rats, but reduces the number of stem cells in adipose tissue. *IFATS Annual Meeting*. 2014:100

49. Traktuev DO, Merfeld-Clauss S, Li J, Kolonin M, Arap W, Pasqualini R, Johnstone BH,

March KL. A population of multipotent cd34-positive adipose stromal cells share pericyte and mesenchymal surface markers, reside in a periendothelial location, and stabilize endothelial networks. *Circulation research*. 2008;102:77-85

50. Traktuev DO, Prater DN, Merfeld-Clauss S, Sanjeevaiah AR, Saadatzadeh MR, Murphy M, Johnstone BH, Ingram DA, March KL. Robust functional vascular network formation in vivo by cooperation of adipose progenitor and endothelial cells. *Circulation research*. 2009;104:1410-1420

51. Merfeld-Clauss S, Gollahalli N, March KL, Traktuev DO. Adipose tissue progenitor cells directly interact with endothelial cells to induce vascular network formation. *Tissue Engineering Part A*. 2010;16:2953-2966

52. Merfeld-Clauss S, Lupov IP, Lu H, Feng D, Compton-Craig P, March KL, Traktuev DO. Adipose stromal cells differentiate along a smooth muscle lineage pathway upon endothelial cell contact via induction of activin a. *Circulation research*. 2014;115:800-809

53. Crisan M, Yap S, Casteilla L, Chen C-W, Corselli M, Park TS, Andriolo G, Sun B, Zheng B, Zhang L. A perivascular origin for mesenchymal stem cells in multiple human organs. *Cell stem cell*. 2008;3:301-313

54. Ter Horst E, Naaijkens B, Krijnen P, Van Der Laan A, Piek J, Niessen H. Induction of a monocyte/macrophage phenotype switch by mesenchymal stem cells might contribute to improved infarct healing postacute myocardial infarction. *Minerva cardioangiologica*. 2013;61:617-625

55. Guisantes E, Fontdevila J, Rodríguez G. Autologous fat grafting for correction of unaesthetic scars. *Annals of plastic surgery*. 2012;69:550-554

56. Klinger M, Caviggioli F, Klinger FM, Giannasi S, Bandi V, Banzatti B, Forcellini D, Maione L, Catania B, Vinci V. Autologous fat graft in scar treatment. *Journal of Craniofacial Surgery*. 2013;24:1610-1615

57. Klinger M, Marazzi M, Vigo D, Torre M. Fat injection for cases of severe burn outcomes: A new perspective of scar remodeling and reduction. *Aesthetic plastic surgery*. 2008;32:465-469

58. Khouri RK, Smit JM, Cardoso E, Pallua N, Lantieri L, Mathijssen IM, Khouri Jr RK, Rigotti G. Percutaneous aponeurotomy and lipofilling: A regenerative alternative to flap reconstruction? *Plastic and reconstructive surgery*. 2013;132:1280-1290

59. Balkin DM, Samra S, Steinbacher DM. Immediate fat grafting in primary cleft lip repair. *Journal of Plastic, Reconstructive & Aesthetic Surgery*. 2014; 67:1644-1650

60. Rigotti G, Marchi A, Galie M, Baroni G, Benati D, Krampera M, Pasini A, Sbarbati A.

Clinical treatment of radiotherapy tissue damage by lipoaspirate transplant: A healing process mediated by adipose-derived adult stem cells. *Plastic and reconstructive surgery*. 2007;119:1409-1422

61. Villani F, Caviggioli F, Klinger F, Klinger M. Rehabilitation of irradiated head and neck tissues by autologous fat transplantation. *Plastic and reconstructive surgery*. 2009;124:2190-2191

62. Chang CC, Thanik VD, Lerman OZ, Saadeh PB, Warren SM, Coleman SR, Hazen A. Treatment of radiation skin damage with coleman fat grafting. *STEM CELLS*. 2007;25:3280-3281

63. Sultan SM, Stern CS, Allen Jr RJ, Thanik VD, Chang CC, Nguyen PD, Canizares O, Szpalski C, Saadeh PB, Warren SM. Human fat grafting alleviates radiation skin damage in a murine model. *Plastic and reconstructive surgery*. 2011;128:363-372

64. Loder S, Peterson JR, Agarwal S, Eboda O, Brownley C, DeLaRosa S, Ranganathan K, Cederna P, Wang SC, Levi B. Wound healing after thermal injury is improved by fat and adipose-derived stem cell isografts. *Journal of Burn Care & Research*. 2015;36:70-76

65. Sultan SM, Barr JS, Butala P, Davidson EH, Weinstein AL, Knobel D, Saadeh PB, Warren SM, Coleman SR, Hazen A. Fat grafting accelerates revascularisation and decreases fibrosis following thermal injury. *Journal of Plastic, Reconstructive & Aesthetic Surgery*. 2012;65:219-227

66. Cuomo R, Zerini I, Botteri G, Barberi L, Nisi G, D'ANIELLO C. Postsurgical pain related to breast implant: Reduction with lipofilling procedure. *In Vivo*. 2014;28:993-996

67. Maione L, Vinci V, Caviggioli F, Klinger F, Banzatti B, Catania B, Lisa A, Klinger M. Autologous fat graft in postmastectomy pain syndrome following breast conservative surgery and radiotherapy. *Aesthetic plastic surgery*. 2014;38:528-532

68. Caviggioli F, Maione L, Forcellini D, Klinger F, Klinger M. Autologous fat graft in postmastectomy pain syndrome. *Plastic and reconstructive surgery*. 2011;128:349-352

69. Caviggioli F, Vinci V, Codolini L. Autologous fat grafting: An innovative solution for the treatment of post-mastectomy pain syndrome. *Breast Cancer*. 2013;20:281-282

70. Salgarello M, Visconti G. The role of sacrolumbar fat grafting in the treatment of spinal fusion instrumentation-related chronic low back pain: A preliminary report. *Spine*. 2014;39:E360-E362

71. Faroni A, Terenghi G, Reid AJ. Adipose-derived stem cells and nerve regeneration: Promises and pitfalls. *Int Rev Neurobiol*. 2013;108:121-136

72. Vaienti L, Gazzola R, Villani F, Parodi PC. Perineural fat grafting in the treatment of painful neuromas. *Techniques in hand & upper extremity surgery*. 2012;16:52-55

73. Marangi GF, Pallara T, Cagli B, Schena E, Giurazza F, Faiella E, Zobel BB, Persichetti P. Treatment of early-stage pressure ulcers by using autologous adipose tissue grafts. *Plastic Surgery International*. 2014;2014

74. Lolli P, Malleo G, Rigotti G. Treatment of chronic anal fissures and associated stenosis by autologous adipose tissue transplant: A pilot study. *Diseases of the Colon & Rectum*. 2010;53:460-466

75. Cantarella G, Baracca G, Forti S, Gaffuri M, Mazzola R. Outcomes of structural fat grafting for paralytic and non-paralytic dysphonia. *Acta Otorhinolaryngologica Italica*. 2011;31:154

76. DeFatta RA, DeFatta RJ, Sataloff RT. Laryngeal lipotransfer: Review of a 14-year experience. *Journal of Voice*. 2013;27:512-515

77. Sataloff RT. Autologous fat implantation for vocal fold scar. *Current opinion in otolaryngology & head and neck surgery*. 2010;18:503-506

78. Cantarella G, Mazzola RF, Mantovani M, Baracca G, Pignataro L. Treatment of velopharyngeal insufficiency by pharyngeal and velar fat injections. *Otolaryngology-- Head and Neck Surgery*. 2011;145:401-403

79. Papa N, Luca G, Sambataro D, Zaccara E, Maglione W, Gabrielli A, Fraticelli P, Moroncini G, Beretta L, Santaniello A. Regional implantation of autologous adipose tissue-derived cells induces a prompt healing of long-lasting indolent digital ulcers in patients with systemic sclerosis. *Cell transplantation*. 2014

80. Hovius SE, Kan HJ, Smit X, Selles RW, Cardoso E, Khouri RK. Extensive percutaneous aponeurotomy and lipografting: A new treatment for dupuytren disease. *Plastic and reconstructive surgery*. 2011;128:221-228

- *reconstructive surgery*. 2013;132:1139-1148

82. Bank J, Fuller SM, Henry GI, Zachary LS. Fat grafting to the hand in patients with raynaud phenomenon: A novel therapeutic modality. *Plastic and reconstructive surgery*. 2014;133:1109-1118

83. Damgaard OE, Siemssen PA. Lipografted tenolysis. *Journal of Plastic, Reconstructive & Aesthetic Surgery*. 2010;63:e637-e638

84. Colonna M, Scarcella M, d'Alcontres F, Delia G, Lupo F. Should fat graft be recommended in tendon scar treatment? Considerations on three cases (two feet and a severe burned hand). *European review for medical and pharmacological sciences*. 2014;18:753-759

85. Merikanto JE, Alhopuro S, Ritsilä VA. Free fat transplant prevents osseous reunion of skull defects: A new approach in the treatment of craniosynostosis. *Scandinavian Journal of Plastic and Reconstructive Surgery and Hand Surgery*. 1987;21:183-188

86. Mojallal A, Lequeux C, Shipkov C, Breton P, Foyatier J-L, Braye F, Damour O.

Improvement of skin quality after fat grafting: Clinical observation and an animal study. *Plastic and reconstructive surgery*. 2009;124:765-774

87. Lockwood TE. Superficial fascial system (sfs) of the trunk and extremities: A new concept. *Plastic and reconstructive surgery*. 1991;87:1009-1018

88. Song AY, Askari M, Azemi E, Alber S, Hurwitz DJ, Marra KG, Shestak KC, Debski R, Rubin JP. Biomechanical properties of the superficial fascial system. *Aesthetic Surgery Journal*. 2006;26:395-403

89. Flynn L. The use of decellularized adipose tissue to provide an inductive microenvironment for the adipogenic differentiation of human adipose-derived stem cells. *Biomaterials*. 2010;31:4715-4724

90. Brown BN, Freund JM, Han L, Rubin JP, Reing JE, Jeffries EM, Wolf MT, Tottey S, Barnes CA, Ratner BD. Comparison of three methods for the derivation of a biologic scaffold composed of adipose tissue extracellular matrix. *Tissue Engineering Part C: Methods*. 2011;17:411-421

91. Wu I, Nahas Z, Kimmerling KA, Rosson GD, Elisseeff JH. An injectable adipose matrix for soft tissue reconstruction. *Plastic and reconstructive surgery*. 2012;129:1247

92. Omidi E, Fuetterer L, Mousavi SR, Armstrong RC, Flynn LE, Samani A. Characterization and assessment of hyperelastic and elastic properties of decellularized human adipose tissues. *Journal of biomechanics*. 2014;47:3657-3663

93. Wang L, Johnson JA, Zhang Q, Beahm EK. Combining decellularized human adipose tissue extracellular matrix and adipose-derived stem cells for adipose tissue engineering. *Acta biomaterialia*. 2013;9:8921-8931

94. Healy C, Allen Sr RJ. The evolution of perforator flap breast reconstruction: Twenty years after the first diep flap. *Journal of reconstructive microsurgery*. 2014;30:121-125

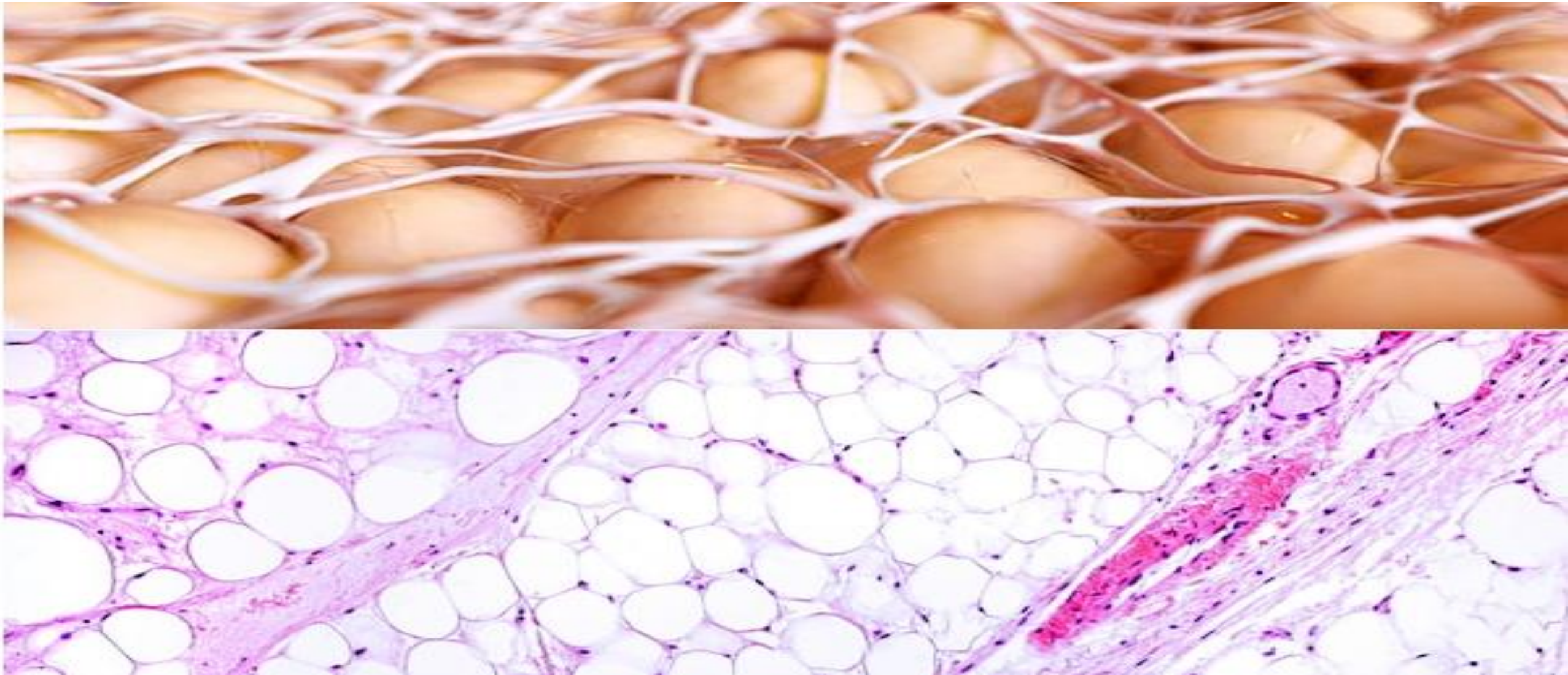
95. LoTempio MM, Allen RJ. Breast reconstruction with sgap and igap flaps. *Plastic and reconstructive surgery*. 2010;126:393-401

96. Erić M, Mihić N, Krivokuća D. Breast reconstruction following mastectomy; patient's satisfaction. *Acta Chir Belg*. 2009;109:159-166

97. Diaz-Flores L, Gutierrez R, Lizartza K, et al. Behavior of In Situ Human Native Adipose Tissue CD34+ Stromal/Progenitor Cells During Different Stages of Repair. Tissue-Resident CD34+ Stromal Cells as a Source of Myofibroblasts. Anatomical record. 2014.

98. Gil-Ortega M, Garidou L, Barreau C, et al. Native adipose stromal cells egress from adipose tissue in vivo: evidence during lymph node activation. Stem cells. 2013;31(7):1309-20.

Enforcement



ENFORCEMENT Priority: Obviously high-risk clinics, *especially*
those that dissuade Pts from getting existing, effective Txs

May 2018: SVF

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF FLORIDA
FT. LAUDERDALE DIVISION

CASE NO.: 18-CV-61047

UNITED STATES OF AMERICA,

Plaintiff,

v.

US STEM CELL CLINIC, LLC, a Florida limited liability company,
US STEM CELL, INC., a Florida profit corporation, and
KRISTIN C. COMELLA and
THEODORE GRADEL, individuals,

Defendants.

COMPLAINT

Plaintiff, the United States of America, by and through undersig

represents as follows:

CHAD A. READLER
Acting Assistant Attorney General
GUSTAV W. EYLER
Acting Director
Consumer Protection Branch
NATALIE N. SANDERS
Trial Attorney
Consumer Protection Branch
U.S. Department of Justice
450 5th Street, NW, Suite 6400-South
Washington, D.C. 20530
Telephone: (202) 598-2208
Facsimile: (202) 514-8742
E-mail: Natalie.N.Sanders@usdoj.gov

Attorneys for Plaintiff
UNITED STATES OF AMERICA

UNITED STATES DISTRICT COURT

FOR THE CENTRAL DISTRICT OF CALIFORNIA

EASTERN DIVISION

UNITED STATES OF AMERICA,

Plaintiff,

v.

CALIFORNIA STEM CELL TREATMENT CENTER, INC., a California corporation, CELL SURGICAL NETWORK CORPORATION, a California corporation, and ELLIOT B. LANDER, M.D., MARK BERMAN, M.D., individuals,

Defendants.

No. 5:18-CV-1005

COMPLAINT FOR PERMANENT INJUNCTION

June 2, 2019: FDA prevails vs. U.S. Stem Cell → *Auer deference*

June 26, 2019: SCOTUS in KISOR v. WILKIE on *Auer deference:*

- Regulation must be **genuinely ambiguous**;
- Agency's **interpretation must be REASONABLE**
- Must reflect agency's authoritative, **EXPERTISE-BASED, fair & considered judgment;**
- Agency must take account of reliance interests & avoid unfair surprise.

Kagan, J:

- "the agency's reading must fall '**within the bounds of REASONABLE interpretation**.'
- **And let there be no mistake: That is a requirement AN AGENCY CAN FAIL."**

- **Courts CANNOT DEFER "to a merely 'convenient litigating position'**
- **or 'post hoc rationalizatio[n] advanced' to 'defend past agency action against attack.'"**

Auer & ADIPOSE

1. **Effective?** Current regulations not curtailing high risk products/modes of delivery.

2. **Reasonable? Expertise-based? Fair? to evaluate adipose as solely structural if it is predominantly NONSTRUCTURAL?**

3. **Given that the "agency can fail," is insisting on a factually inaccurate interpretation a recipe for success?**

Solving Problems … or causing them?

1. **FACTS: HCT/P's characteristics & components w/ "basic function or basic functions" = BOTH "structural" & "cell or nonstructural" under regs.**

2. **FDA as BASIC FUNCTION CZAR? [**
    1. **DRAFT: Basic Function of Breast = Lactation.**
    2. **More problems in defining basic functions of amnion, skin and more**

3. **NONSTRUCTURAL ADIPOSE THERAPIES UNEVALUATED and unused simply because the FDA has labeled adipose as doing one thing when it actually does the opposite (or at times, does both).**

4. **Many inconsistencies: Adipose MSCs from subcutaneous fat = nonhomlogous**
5. **Same cells from Bone Marrow**

FDA's "Adipose as Solely Structural" Strategy

- **As applied to adipose, FDA's interpretation can backfire**
- **Unnecessarily risks defeat**
- **RISK: Powerful defense to dubious clinics bent on their dubious ways.**
- **RISK: Precludes meaningful evaluation of risks & safety of promising and often low risk autologous HCT/P therapies**

FDA's "Adipose as Solely Structural" Strategy

- **Doing the wrong thing for the right reasons** warrants heightened scrutiny, not *Auer* deference.

- This unnecessarily **risks defeat**
- For comprehensive framework & multipronged strategy of litigation, enforcement discretion and interpretive guidance to succeed…

- **FDA must rethink and revise** current guidance & basic approach to **regulating HCT/Ps with multiple functions.**
- **ESPECIALLY NONSTRUCTURAL ADIPOSE!**

Easy to criticize, but what's a Regulator to do?

1. **Improve the Regs – Revise & Supplement as needed**
2. **Respect& enforce according to regs' definitions**
3. **Respect biology**
4. Collaborate with expert ass'ns to understand:
    a. biology & clinical translation
    b. patient registries
    c. certification, accreditation, registration

5. **Re-vamp enforcement strategy**

    → **TOO MUCH for FDA & unfair to FDA, patients & providers…**

Enforcement: Consider Stem Cell Strike Force

- **Interagency teams → Investigators + Prosecutors**
- **Collaboration among Federal and State Agencies, Investigators, Law Enforcement**
- **Focus on worst offenders in high intensity regions**
- **Data analysis → Target suspicious patterns + Emerging schemes + Shape-shifting products & entities**
  - **1970's: DOJ's Organized Crime Strike Force to enforce newly-enacted RICO Act**
  - **Today: DOJ Strike Forces**
  - **National Health Care Fraud Strike Force**
  - **Medicare Fraud Strike Force**
  - **Cyber-Digital Strike Force**
  - **Organized Crime Drug Enforcement Task Force**
  - **Transnational Elder Fraud Strike Force**
  - **Procurement Collusion Strike Force**

Health Care Fraud Unit: Mission

- **Focus solely on the prosecution of health care fraud cases**
  - **Emphasis:** cases involving patient harm & large loss to public fisc
- **Identify**, **respond to**, and **prosecute** emerging fraud trends across the U.S.
- **Train** AUSAs and agents on best practices for investigating and prosecuting HCF cases
- **Analyze** data to:
  - Identify aberrant billing levels in health care fraud hot spots and
  - Target suspicious billing patterns and schemes that migrate from one community to another

FY 2016 Statistics

- 241 individuals charged
- 146 charging documents
- 156 individuals convicted
  - Average sentence of 53 months
- $2.1 billion loss to federal health care programs
- 1 corporate resolution ($512 million total resolution amount)
- Executed 2016 National Health Care Fraud Takedown
- Executed 2016 National Health Care Fraud Training Conference

“What we’re playing now is a game of Whack-a-Mole.”

Peter Marks, “Bad Batch” podcast, Nov. 13, 2019

“We’ve got major issue here, and we have to triage....”

Thank you.

FDA Regulation of Adipose Stem Cell Therapies: Separating Fat from Fiction

Mary Ann Chirba, Professor, Boston College Law School

Public Perception and Policy Development in Consent Standards for Human Research—How Competing Views on Public Goods and Private Interests Shape Data Sharing, Big Data Research, and Other Activities Using Human Data and Materials”

Valerie Bonham, Counsel, Ropes & Gray LLP

Discussant: **Kalah Auchincloss**, Senior Vice President, Regulatory Compliance & Deputy General Counsel, Greenleaf Health, LLC
Moderator: **Barbara Binzak Blumenfeld**, Shareholder, Buchanan Ingersoll & Rooney PC

FDLI