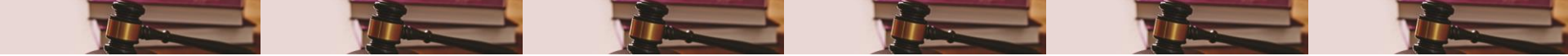
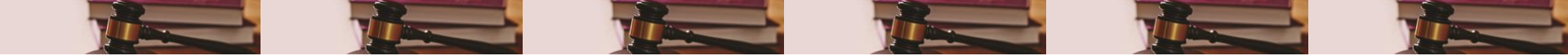


Unique Compliance and Enforcement Issues with Cell and Gene Therapies

Barbara A. Binzak Blumenfeld, Shareholder, Buchanan Ingersoll & Rooney PC
Areta Kupchyk, Partner, Foley Hoag LLP
Mark Levi, Senior Consultant, RCS Regulatory, Parexel International
Moderated by **Kalah Auchincloss**, Senior Vice President, Regulatory Compliance, and Deputy General Counsel, Greenleaf Health, Inc.

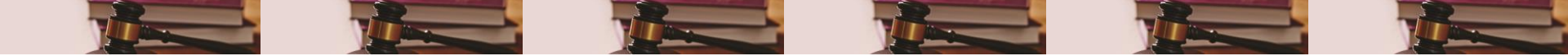
FDLI



Unique Compliance and Enforcement Issues with Cell and Gene Therapies

Moderated by **Kalah Auchincloss**, Senior Vice President, Regulatory Compliance, and Deputy General Counsel, Greenleaf Health, Inc.

FDLI



FDLI Enforcement Conference

Cell and Gene Therapies
Guidance on HCT/Ps and Production Scale Up

Mark Levi, PhD, PAREXEL Intl.

FDLI

Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)

- HCT/Ps = defined in 21 CFR 1271.3(d) as articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient
- Examples of HCT/Ps include, but are not limited to, bone, ligament, skin, dura mater, heart valve, cornea, hematopoietic stem/progenitor cells derived from peripheral and cord blood, manipulated autologous chondrocytes, epithelial cells on a synthetic matrix, and semen or other reproductive tissue
  - Eight articles are not considered HCT/Ps: Human organs; whole blood; secreted human products; bone marrow for homologous use; ancillary products; cells, tissues, and organs from animals other than humans; in vitro diagnostics; and blood vessels attached to organs for transplant

Guidance Documents on HCT/Ps

- Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs); corrected July 20, 2018
  - Excellent detail on the information needed for eCTD Module 3
- Long Term Follow-up After Administration of Human Gene Therapy Products; issued July 2018
  - Recommendations for up to 15 years of follow up; first 5 years and years 5-15

Guidance Documents

- Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use; corrected Dec. 2017
  - Current thinking on 21 CFR 1271.10(a)(1) criterion of minimal manipulation and the (a)(2) criterion of homologous use
- Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up; July 2018
  - Current thinking on testing (frequency, amounts, assays) of Master Cell Banks, vector harvest material, and ex vivo transduced cells

Additional Guidance Documents

- Human Gene Therapy for Hemophilia; July 2018
  - Updated FDA thinking on activity assays and considerations for clinical trials, endpoints
- Human Gene Therapy for Rare Diseases; July 2018
  - Updated FDA thinking on CQA and their variability, information from a natural history study, clinical trial design and (surrogate) endpoints
- Human Gene Therapy for Retinal Disorders; July 2018
  - Includes additional CMC considerations and aims to reduce potential clinical trial bias

Deviation Reporting for Human Cells, Tissues, and Cellular and Tissue-Based Products Regulated Solely Under Section 361 of the Public Health Service Act and 21 CFR Part 1271; September 2017

The following are core CGTP requirements:

- Donor-eligibility determinations, donor screening, and donor testing (21 CFR 1271.50, 1271.75, 1271.80, and 1271.85)
- Facilities (21 CFR1271.190(a) and (b))
- Environmental control (21 CFR1271.195(a))
- Equipment (21 CFR 1271.200(a))
- Supplies and reagents (21 CFR1271.210(a) and (b))
- Recovery (21 CFR1271.215)
- Processing and process controls (21 CFR1271.220)
- Labeling controls (21 CFR1271.250(a) and (b))
- Storage (21 CFR 1271.260(a) through (d))

What and Who Must Report?

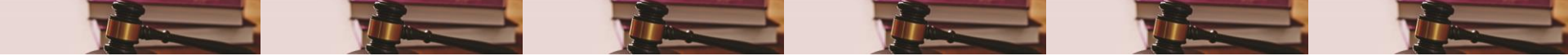
- Defined in 21 CFR 1271.3(dd) as an event:
  - 1.That represents a deviation from applicable regulations in 21 CFR Part 1271 or from applicable standards or established specifications that relate to the prevention of communicable disease transmission or HCT/P contamination

  or

  - 2. That is an unexpected or unforeseeable event that may relate to the transmission or potential transmission of a communicable disease or may lead to HCT/P contamination
- The guidance also contains examples of who must report a deviation, how to report, and when one is not required

Cell and Gene Therapy Scale-Up Issues

- Process- and manufacturer-specific
- Requires tedious work to resolve



Unique Compliance and Enforcement Issues with Cell and Gene Therapies

Areta Kupchyk
Partner
Co-Chair of the FDA Group
Foley Hoag LLP

Enforcement, Litigation, and Compliance Conference
December 2018

FDLI

Cellular and Tissue-Based Products

Human Cell, Tissue, and Cellular and Tissue-Based Products (HCT/Ps) Framework

- §361 of the Public Health Service Act (PHS Act)
  - Four criteria must be met
  - No pre-marketing submission/approval required
  - HCT/P Good Tissue Practice under 21 CFR Part 1271
- §351 of the PHS Act
  - Criteria not met = Biological Product (or Device; Combination Biological/Device)
  - Premarket approval = IND and BLA
  - Current Good Manufacturing Practice (cGMP) Regulations
    - 21 CFR Parts 210 & 211

HCT/P Criteria for Regulation as a §361 Product

Four criteria for regulation solely under § 361 of the PHS Act and 21 CFR Part 1271

a. Minimally manipulated;

b. Intended for a homologous use only as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent;

c. Not combined with another article, (except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of the agent does not raise new clinical safety concerns with respect to the HCT/P); **AND**

d. Either:

i. Do not have a systemic effect and are not dependent upon the metabolic activity of living cells for the primary function; **OR**

ii. Have a systemic effect or are dependent upon the metabolic activity of living cells for their primary function, **AND:**

a) Are for autologous use;

b) Are for allogeneic use in a first or second-degree relative; **OR**

c) Are for reproductive use

FDA Final 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

Finalized November 2017
Corrected December 2017

Minimal Manipulation

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*
- *Original relevant characteristics* generally include the *properties of that tissue in the donor that contribute to the tissue's function or functions*.
  - *Structural Tissue Examples*:
    - Skin & Bone
    - Amniotic membrane and umbilical cord
    - Blood vessel
    - Articular cartilage & non-articular cartilage
    - Tendon or ligament
    - *Adipose tissue*

Original Relevant Characteristics

Guidance states:

- Original relevant characteristics of structural tissues generally include the properties of that tissue in the donor that contribute to the tissue's function or functions.
- A tissue characteristic is "original" if it is present in the tissue in the donor.
- A structural tissue characteristic is "relevant" if it could have a meaningful bearing on the tissue's utility for reconstruction, repair, or replacement.
- The structural tissue's utility for reconstruction, repair, or replacement relates to how that tissue functions in the donor.
- Examples of relevant characteristics of structural tissues include strength, flexibility, cushioning, covering, compressibility, and response to friction and shear.

Isolating Cells from Structural Tissue

Guidance states:

- **If you isolate cells from structural tissue, the definition of minimal manipulation for structural tissue applies, regardless of the method used to isolate the cells.**
- Why? Because the assessment of whether the HCT/P is a structural tissue or cellular/nonstructural tissue is based on the characteristics of the HCT/P ***as it exists in the donor, prior to recovery*** and any processing that takes place.

Adipose Tissue: Structural Tissue

Guidance states:

- Adipose tissue is connective tissue composed of clusters of cells (adipocytes) surrounded by a reticular fiber network & interspersed small blood vessels, divided into lobes & lobules by connective tissue septa.
- Adipose tissue provides *cushioning* and *support for other tissues*, including the skin and internal organs, stores energy in the form of lipids, and insulates the body.
- Example: Person recovers adipose tissue by tumescent liposuction and processes *(e.g., enzymatically digests, mechanically disrupts, etc.)* it to isolate cellular components *(with or without subsequent cell culture or expansion),* commonly referred to as **stromal vascular fraction** (potential source of adipose-derived stromal/stem cells). The SVF product is regulated as a structural tissue.

Minimal Manipulation

For cells or nonstructural tissues

- Processing that does not alter the *relevant biological characteristics* of cells or tissues.
- *Relevant biological characteristics* generally include the properties of the cells or nonstructural tissues in the donor that contribute to the cells or tissue's function(s).

Relevant Biological Characteristics

Guidance states:

- Cells or nonstructural tissues are generally those that serve predominantly *metabolic* or other *biochemical roles* in the body such as hematopoietic, immune, and endocrine functions.
- Examples of relevant biological characteristics of cells or nonstructural tissues include *differentiation* and *activation state*, *proliferation potential*, and *metabolic activity*.

Cells or Nonstructural Tissues

Examples :

- Reproductive cells or tissues *(e.g., oocytes)*
- Hematopoietic stem/progenitor cells *(e.g., cord blood)*
- Lymph nodes and thymus
- Parathyroid glands
- Peripheral nerve
- Pancreatic tissue

Excluded:

- Secreted or extracted body fluids, such as amniotic fluid, milk, collagen, and cell factors.

But:

- *Cells from* secreted body fluids *are* considered HCT/Ps and minimal manipulation for cells or nonstructural tissues applies

Homologous Use

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(s)* in the recipient as in the donor *as reflected by the labeling, advertising, and other indications of a manufacturer's objective intent*.

- The affected cells or tissues in the recipient do not have to be identical to the donor's cells or tissues.

Homologous Use Labeling

… as reflected by the labeling, advertising, and other indications of a manufacturer's objective intent.

- Objective intent is determined by :
  - The *expressions* of the manufacturer or its representatives, such as
    - Labeling claims, advertising matter, or oral or written statements by the manufacturer or its representatives.
  - The *circumstances* surrounding the distribution of the article
    - Suggest or imply a use for which it's neither labeled nor advertised, e.g., product indicated for orthopedic conditions but sales are to cardiologists.

FDA's Enforcement Discretion Policy

Guidance states:

- If more than minimally manipulated or not homologous, IND or BLA required.
- FDA is exercising enforcement discretion until **January 2021** (36 months after guidance issued) *provided that use of the HCT/P does not raise reported or potentially significant safety concerns*:
  - Enforcement priority on higher risk HCT/Ps based on route and site of administration (e.g., administered by intravenous injection or infusion, aerosol inhalation, intraocular injection, or injection or infusion into the central nervous system)
  - By comparison, lower risk may fall under enforcement discretion (e.g., those administered by intradermal, subcutaneous, or intra-articular injection).
- FDA continues to reassess application of HCT/P regulatory framework for regenerative medicine products based on emerging scientific evidence.

Product/Violations Frequently Cited

- **Adipose Tissue** - Stem Cells -- not a 361 Product
  - *More than minimally manipulated* (processed to obtain ***stromal vascular fraction (SVF)***) – alters original relevant characteristics
  - *Not homologous* because not intended for *cushioning*; instead intended to treat, for example, Alzheimer's disease, Crohn's disease, diabetes, fibromyalgia, spinal cord injury, COPD, MS, muscular dystrophy, Parkinson's disease, peripheral neuropathy, ALS, and rheumatoid arthritis.
  - *Recent Untitled Letter issued July 17, 2018; Injunctions sought in May 2018 against 2 stem cell clinics; Warning Letters issued in January 2018 and August 2017*
  - cGMP violations also cited
    - Lack of adequate donor screening/testing, inadequate written procedures and production and process controls that raise the risk of microbial contamination, failure to have & follow procedures for receipts, identification, storage, handling, sampling, testing, approval or rejection of components, containers, closures

Injunctions Sought Against Stem Cell Clinics

- DOJ/FDA are seeking permanent injunctions against two stem cell clinics and key management individuals marketing SVF treatments (May 9, 2018)
  - ***California Stem Cell Treatment Center, Inc. and Cell Surgical Network Corporation***
  - ***US Stem Cell Clinic***
    - Marketing unapproved adipose-derived SVF for the treatment of cancer, ALS, stroke, arthritis, MS, macular degeneration, Parkinson's disease, COPD, diabetes.
    - Significant cGMP deviations
    - Warning Letter – August 24, 2017
- Seizure of Vaccinia Virus Vaccine (Live), a combination smallpox vaccine and SVF that had been administered to immune-compromised patients (August 2017)

Other Products & Violations

- **Reproductive Tissue** (oocytes and semen)
  - Four Warning Letters (2018, 2017, 2016, 2014)
  - Failure to test donor specimen for evidence of infection, failure to review donor's relevant medical records, failure to complete donor physical assessment, failure of responsible person determining donor eligibility, inadequate donor medical history interview questions.
- **Amniotic Tissue-Based Products**
  - *More than minimal manipulation* (morselization, micronization)
  - *Non-homologous use* – enhances tissue healing and repair, *e.g.,* adhesion barriers around nerve repairs and for chronic tendinitis/tendinosis, intra-articular injection for chronic inflammatory disease and degenerative joint disease
    - Homologous use would be *covering*, protecting the fetus from the surrounding maternal environment, serving as a selective barrier for the movement of nutrients between external and in utero environment, retaining fluid in utero.

Other Cellular Products & Violations

- **Mesenchymal stem cells (MSCs)**
  - *U.S. v. Regenerative Sciences LLC* (February 2014)
  - Extraction of a sample of a patient's bone marrow or synovial fluid.
- **Injectable, micronized amniotic/chorionic-based products**
  - 2013 issued 6 Untitled Letter
- **Multipotent adult progenitor cells**

FDA's Enforcement Discretion Policy

- Enforcement may begin **January 2021**
- Until then, actions may be taken when use of the HCT/P raises "significant safety concerns."
  - **High risk HCT/Ps** include administered by intravenous injection or infusion, aerosol inhalation, intraocular injection, or injection or infusion into the central nervous system)
  - **Low risk HCT/Ps** include those administered by intradermal, subcutaneous, or intra-articular injection.

FDLI Enforcement, Litigation, and Compliance Conference

Unique Compliance and Enforcement Issues with Cell and Gene Therapies

December 12, 2018

Barbara A. Binzak Blumenfeld, Ph.D., J.D., M.A.
Shareholder – FDA & Biotechnology
Buchanan Ingersoll & Rooney PC

Key Question:

How and Why Have Federal Agencies Recently Accelerated Enforcement Actions Against Stem Cell Products, Manufacturers, and Physicians?

Stem Cells – FDA Enforcement

- Historically: Few warning letters, little case law
  - U.S. v. Regenerative Sciences, LLC (878 F.Supp.2d 248 (D.D.C. 2012); 741 F.3d 1314 (U.S. Ct. App. DC Cir. 2014))
  - "Cultured Regenexx Procedure"
- Today: More scrutiny, more enforcement actions
  - More "clinics," advertising, press, and claims
  - Federal agencies taking different strategies, targeting different issues
    - Marketing unapproved drugs – Two FDA/DOJ lawsuits in CA, FL (May 2018)
    - Unsupported claims – FTC settlement with physician/two companies in CA (October 2018)
    - Marketing unapproved drugs, failure to comply with mfrg. reqmts. – FDA warning letters

There are a small number of unscrupulous actors who have seized on the clinical promise of regenerative medicine, while exploiting the uncertainty, in order to make deceptive, and sometimes corrupt, assurances to patients based on unproven and, in some cases, dangerously dubious products. These dishonest actors exploit the sincere reports of the significant clinical potential of properly developed products as a way of deceiving patients and preying on the optimism of patients facing bad illnesses. This puts the entire field at risk…. These so-called treatments run afoul of the FDA's legal and regulatory framework governing this new field (emphasis added).

Statement from FDA Commissioner Scott Gottlieb, M.D. on the FDA's new policy steps and enforcement efforts to ensure proper oversight of stem cell therapies and regenerative medicine (August 28, 2017)

Marketing Unapproved Drugs – FDA/DOJ Actions

- Case #1: US Stem Cell Clinic, LLC
  - March 16, 2017: *NEJM* article on patient vision loss; covered in popular press
  - April-May 2017: FDA inspection
  - August 24, 2017: FDA warning letter
  - August 28, 2017: FDA posts warning letter; covered in popular press
  - **August 28, 2017: FDA pre-announces regenerative medicine framework**
  - August 29, 2017: Clinic posts public response on website
  - **November 16, 2017: FDA releases regenerative medicine framework**
  - May 9, 2018: Suit for permanent injunction – U.S. v. US Stem Cell Clinic, LLC (Case No. 18-cv-61047 (US Dist. Ct. S.D.FL (2018))

Marketing Unapproved Drugs – FDA/DOJ Actions

– Case #2: California Stem Cell Treatment Center, Inc.

- December 30, 2015: Warning letter to one of defendants' affiliates
- February 2017: Defendants admit continuing actions during interview
- July 2017: FDA inspection; defendants' written response
- August 25, 2017: U.S. Marshals seize 5 vials of Vaccinia Virus, Live
- **August 28, 2017: FDA pre-announces regenerative medicine framework**
- August 31, 2017: Defendant call with FDA
- October 17, 2017: FDA response to request for meeting
- **November 16, 2017: FDA releases regenerative medicine framework**
- May 9, 2018: Suit for permanent injunction – U.S. v. California Stem Cell Treatment Center (Case No. 5:18-cv-1005 (US Dist. Ct. C.D.CA (2018))

Unsupported Claims – FTC Settlement

- October 18, 2018: Settlement of first FTC action involving stem cells (CA)
  - Dr. Bryn Jarald Henderson, D.O.; Regenerative Medical Group; Telehealth Medical Group (Case No. 8:18-cv-01838 (US Dist. Ct. C.D.CA (2018))
  - Deceptive advertising of "amniotic stem cell therapy" to treat multiple serious diseases
  - Initial cell injections = $9,500-$15,000
  - "Booster" injections = $5,000-$8,000 each
  - Order prohibits misrepresenting that any product or service (1) cures, mitigates, or treats any disease; and (2) is comparable or better than conventional medical treatments (unless true and supported by competent and reliable evidence)
  - $3.31M judgment; partially suspended after pay $525K to FTC
  - Defendants must notify all current and former patients of settlement within 30 days

Marketing Unapproved Drugs, Mfrg. Failures – FDA Warning Letters

Failure to Comply with 21 C.F.R. Part 1271; *NOT* Marketing an Unapproved New Drug

- May 7, 2018: Emmett F. Branigan, MD, PS, Inc. (WA)
- May 24, 2018: The Fertility Partnership LLC (MO)
- October 30, 2018: Globus Medical (PA)/Human Biologics of Texas (TX)

Failure to Comply with 21 C.F.R. Part 211; Marketing an Unapproved New Drug

- January 3, 2018: American CryoStem Corporation (NJ)
- October 31, 2018: StemGenex Biologic Laboratories, LLC (CA)

FDA Enforcement Discretion

- November 2017: Final FDA Guidance Document, "Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use"
  - Provides manufacturers time to determine if IND or BLA required
  - Enforcement discretion until November 2020 for HCT/Ps that require IND/BLA – if no safety concerns
  - FDA to focus enforcement efforts on higher-risk products
    - Particular routes of administration (*e.g.,* IV injection/infusion; intraocular injection)
    - Allogeneic use
    - Particular diseases (*e.g.,* serious and/or life-threatening)

Enforcement Takeaways

- Stem cell products, claims, and regulation ripe for confusion
- Increasingly aggressive advertising and claims
- FDA does not regulate practice of medicine
  - Remove HCT/P from an individual and implant such HCT/Ps into same individual during same surgical procedure – NARROW EXEMPTION (21 C.F.R. § 1271.15(b))
- FDA does regulate products and articles used during practice of medicine
  - Off-label use of approved product vs. use of unapproved product
- Expect continued enforcement actions from FDA, DOJ, FTC

Buchanan Ingersoll & Rooney PC

Thank you

Barbara A. Binzak Blumenfeld, Ph.D., J.D., M.A.

Phone: 202-452-7906

Email: barbara.binzak@bipc.com

FDLI Food and Drug Law Institute