Greenleaf Health

Cell & Gene Therapy Compliance

Kalah Auchincloss
EVP & Deputy General Counsel
Greenleaf Health, Inc.

Regenerative Medicine Definitions

Gene Therapy

Transfer of **genetic material**, usually in a carrier or vector, and the uptake of the gene into the appropriate cells of the body to modify a patient's genetic material to treat a disease

- Gene addition, gene correction, gene silencing
- CRISPR/Cas9, other technologies

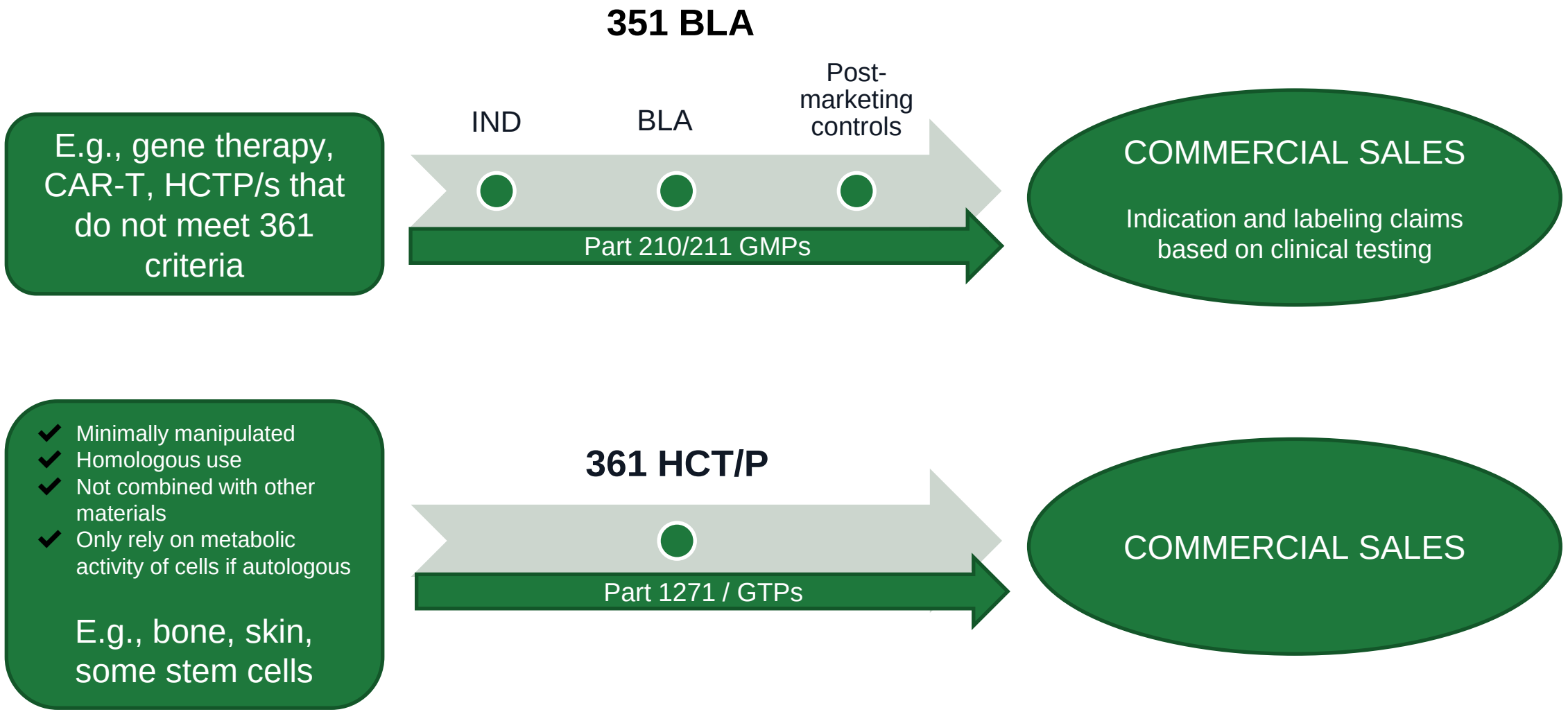
Cell Therapy

Transfer of **cells** with certain functions into a patient to treat a disease

- Autologous (cells from patient)
- Allogeneic (donor cells)
- CAR-T cells, stem cells, others

Clinical benefit of CGT products comes from having a **controlled manufacturing process** and **understanding critical quality attributes** because **product quality, safety, and efficacy are inextricably linked**

Regulatory Pathways



Greenleaf Health

Cell and Gene Therapy

21

21 CGT products approved in the US

https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products

~400

Approx. 400 IHCTOA letters sent to stem cell companies marketing likely violative products under 361 (fraudulent claims, likely require BLA, etc.)

>900

More than 900 INDs as of December 2019

500,000

By 2030 CBER predicts

- ✓ 40 to 60 product launches
- ✓ More than 500,000 patients treated

CHALLENGES

CGT products come with unique challenges

- ✓ Nonclinical development
- ✓ Clinical development
- ✓ CMC & Manufacturing
- ✓ Product access

Greenleaf Health

Regenerative Medicine Framework

- Multiple guidance documents (first batch in 2017)
  - Clarify existing regulations to make it easier for sponsors to determine if they need to obtain premarket authorization for their products
    - E.g., *Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use*
    - E,g., *Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception*
  - Expedite the development and approval of safe and effective innovative regenerative medicine therapies and associated devices
    - E.g., *Expedited Programs for Regenerative Medicine Therapies for Serious Conditions*
  - Guidance on clinical development and regulatory issues
    - E.g., *Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)*
    - Disease specific guidances
- https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products

Enforcement: HCT/P

Historically, not many stem cell products, unclear what constituted "minimal manipulation" or "homologous use" = few enforcement actions

- Recent proliferation of stem cell products, including potentially fraudulent products and marketing for unproven claims
- Are these subject to § 361 (GTPs) or § 351 (BLAs)?
  - *FDA Guidance, Regulatory Considerations for HCTP/s: Minimal Manipulation & Homologous Use (December 2017)*
    - Further clarity on minimal manipulation and homologous use
    - If more than MM or not homologous use = BLA required
    - Enforcement discretion until January 2021 (extended to May 31, 2021)
- Stepped up attention and risk based enforcement actions since guidance issued

Future

FDA is Implementing Regenerative Medicine Framework

- Use of expedited programs and RMAT designation
- Public and individual sponsor meetings (INTERACT)

FDA is expanding its cell & gene therapy review staff

- Guidance to assist with CGT clinical development challenges?
- Additional meetings/collaborations with industry?

May 31, 2021 end of enforcement discretion for stem cells

- More enforcement actions coming?
  - Ongoing litigation
  - WLs? Seizures? Injunctions?

Kalah Auchincloss

Greenleaf Health, Inc.

Kalah.Auchincloss@greenleafhealth.com

FDLI REGENERATIVE MEDICINE CONFERENCE:

ENSURING REGENERATIVE THERAPY PRODUCT COMPLIANCE WITH FDA

June 9, 2021

Melissa J. Mendoza, JD
Deputy Office Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
United States Food and Drug Administration

Regenerative Medicine Products: An Important Distinction

- Products Marketed in Violation of the Law
- Products Being Developed Lawfully

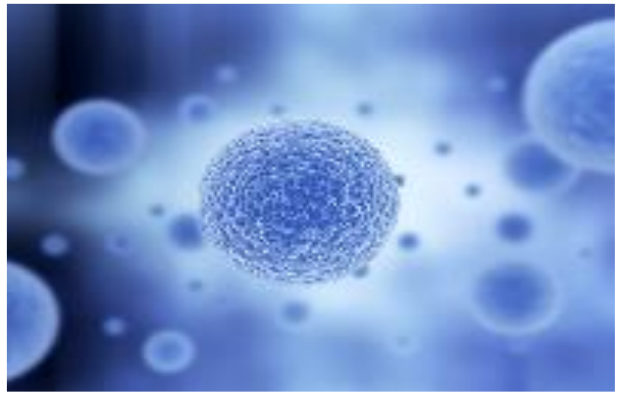
Notable Developments Involving Products Marketed in Violation of the Law

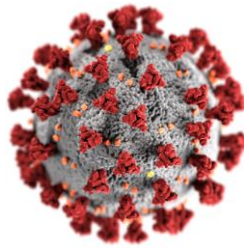
- Compliance and Enforcement Policy for Certain HCT/Ps: Expired on May 31, 2021
- Enforcement Action Update
- COVID-Related Warning Letters

Enforcement Action Update

- *United States v. US Stem Cell Clinic LLC et al.* (11th Cir.)

- *United States v. California Stem Cell Treatment Center, Inc., Cell Surgical Network Corporation, et al.* (C.D. Cal.)





COVID-Related Warning Letters

"Stem Cells For COVID-19 . . . Lattice Biologics CEO injects himself with 1 million stem cells to test safety and efficacy." **- Lattice Biologics, Ltd**

"In response to the current health crisis, our team would like to provide you with an opportunity to receive your own stem cells. . . . Having a frozen line of one's own personal mesenchymal stem cells could prove life-saving should someone become a victim of the current viral pandemic." **- Sparrow Health & Performance, LLC**

"Exosomes are able to help in the fight against COVID-19. Treatments are available right now which have been shown to strengthen your immune system against Novel Coronavirus, and aid in mitigating advanced symptoms such as acute respiratory distress syndrome. Learn more at www.regenerativesolutionsnj.com/virus-protection and call us at 732-548-2000 to schedule an immediate appointment!"
- Regenerative Solutions of New Jersey

"…we have a COVID Relief Stimulus Program where if you are in financial hardship, but you do want to have stem cell therapy . . . , you could use your relief check and apply that towards a full stem cell treatment." **- Dr. Yoo, 21st Century LaserSTEM Pain & Regenerative Medicine Institute**

Lawfully Developed Products

- Thank you
- CBER stands ready to work with you
- INTERACT
- CMC Inquiries: Contact OCOD; Role of OCBQ/DMPQ/ARB; Be specific!

Public Access to CBER

Consumer Affairs Branch (CAB)

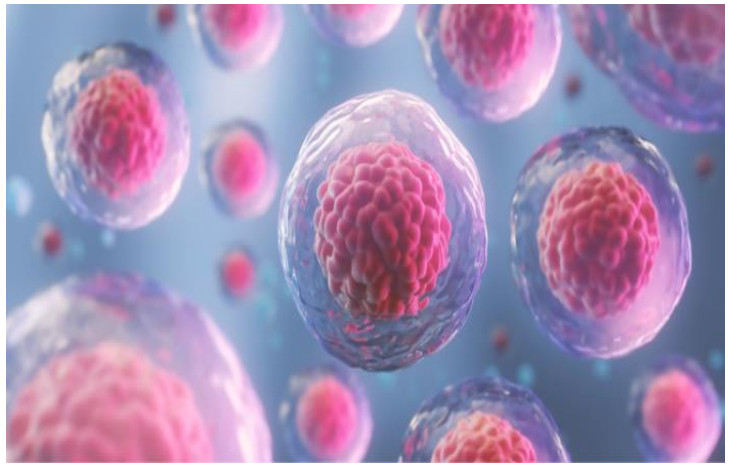
Email: ocod@fda.hhs.gov

Phone: (301) 827-3821

Manufacturers Assistance and Technical Training Branch (MATTB)

Email: industry.biologics@fda.gov

Phone: (301) 827-4081



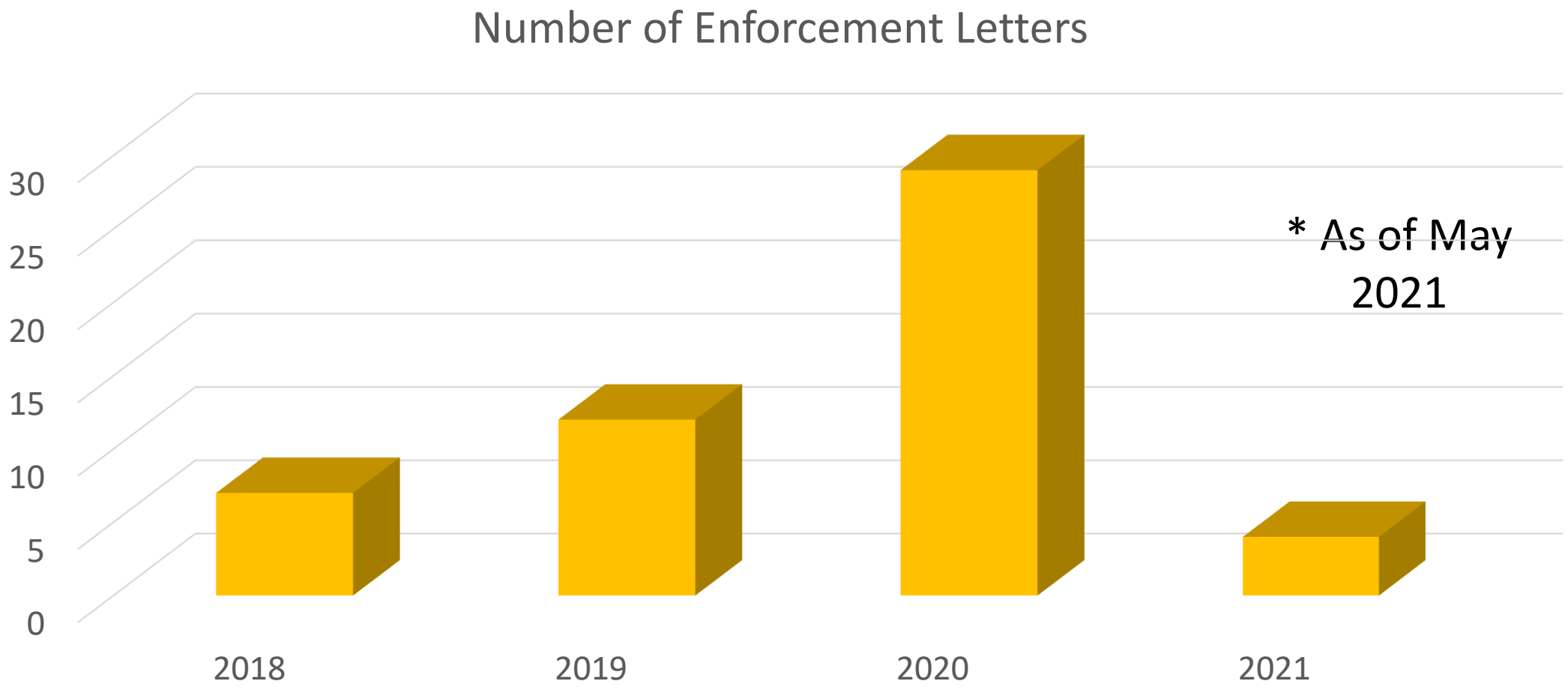
SheppardMullin

FDLI - Regenerative Medicine: Regulatory, Legal, and Compliance Challenges for Cell and Gene Therapies

Enforcement and Compliance Trends

Allison Fulton
Sheppard Mullin Richter & Hampton LLP
June 9, 2021

Enforcement & Compliance Trends



Source: https://www.fda.gov/vaccines-blood-biologics/enforcement-actions-cber/bimoteam-biologicsinternet-surveillanceother and search of FDA Warning Letters

Insight from Warning and Untitled Letters

- Observations in Untitled & Warning Letters
  - Products derived from umbilical cord blood and stem cells (non-homologous use) that lack BLA / IND
  - Fertility clinics
  - COVID-19 claims

"On June 3, 2020, during a chat on your [Company] Facebook page, you were specifically asked, "Do you offer any stem cell products for prevention of COVID?" You stated the following in response to the aforementioned question:

"Yes we do offer preventative treatments that can help boost the immune system and fortify lungs against viruses."

Insight form Warning and Untitled Letters

- Observations in Untitled & Warning Letters
  - Lack of donor screening for communicable diseases
  - Inadequate aseptic controls for manufacturing
    - Media fills
    - Gowning
    - Aseptic technique
    - Equipment cleaning validation

"The deviations in manufacturing processes observed as well as those noted in documents collected during the inspection indicate that the use of your products raises potential significant safety concerns.

For example, [company's] deficient donor eligibility practices, inadequate aseptic practices, and deficient environmental monitoring, as described below, pose a significant risk that your products may be contaminated with microorganisms or have other serious product quality defects."

Insight from Warning and Untitled Letters

- Observations in Untitled & Warning Letters
  - Unsubstantiated claims on web sites, Facebook posts
  - Patient testimonials

"Not FDA approved," "experimental," and provided by IV infusion for patients, including those with "various chronic conditions" such as "auto-immune problems, lupus, rheumatoid arthritis, psoriasis ... lung problems, COPD, heart issues ... or dementia .... " April 18 Facebook posting at:"

“I was diagnosed with COPD 10 years ago…I received an Umbilical Stem Cell IV infusion and I have never felt better.”

Other Compliance Issues

- Importing/exporting of cellular tissue products
- Impact of enforcement discretion policy