



Cell and Gene Therapy Compliance and Enforcement

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PRODUCT DEFINITIONS

DRUG – 21 U.S.C. § 321(g)(1) [Federal Food, Drug, and Cosmetic Act]

- if it is “intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease” [§ 321(g)(1)(B)], or
- is “intended to affect the structure or any function of the body of man or other animals” [§ 321(g)(1)(C)].

Biological Products – 42 U.S.C. § 262(i) [Public Health Service Act]

- “virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product . . . , applicable to the prevention, treatment, or cure of a disease or condition of human beings.”
- A product may be both a drug and a biological product.

HCT/Ps – 21 C.F.R. § 1271.3(d)[Human cells, tissues, or cellular or tissue-based products]

- “articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient.”

Regulation of HCT/Ps: 21 C.F.R. Part 1271

Products Regulated as 361 HCT/Ps

- Meet *all* the criteria set forth in 21 C.F.R. § 1271.10(a)
- Regulated solely under PHS Act Section 361 (42 U.S.C. § 264) and 21 C.F.R. § 1271
- **Not** regulated as drugs, devices, and/or biological products, so no premarket review is required
- E.g.s, bone, ligaments, tendons, corneas, skin, arteries and veins

Products Regulated as Drugs, Devices, and/or Biological Products

- Do not meet the criteria in 21 C.F.R. § 1271.10(a)
- **Are** regulated as either a drug, device, and/or biological product under the FD&C Act, and/or Section 351 of the PHS Act (42 U.S.C. § 262), and applicable regulations, including 21 C.F.R. Part 1271
- Premarket review is required
- E.g.s, cultured cartilage or nerve cells, stromal vascular fraction, “flowable” amniotic membrane

Regulation of HCT/Ps: 21 C.F.R. Part 1271

Part 1271's Requirements

- Subpart B – Procedures for Registration and Listing
21 C.F.R. §§ 1271.21 – 1271.37
- Subpart C – Donor Eligibility
21 C.F.R. §§ 1271.45 – 1271.90
- Subpart D – Current Good Tissue Practice
21 C.F.R. §§ 1271.145 – 1271.320
- Subpart E – Additional Requirements for Establishments
21 C.F.R. §§ 1271.330, 1271.350 (Reporting), 1271.370 (Labeling)
- Subpart F – Inspection and Enforcement of Establishments
21 C.F.R. §§ 1271.390, 1271.400 (Inspections), 1271.420 (HCT/Ps offered for import), 1271.440 (Orders of retention, recall, destruction, and cessation of manufacturing).

Case Law

- **Injunctions Pursuant to 21 U.S.C. § 332(a)**

- *United States v. Regenerative Sciences LLC*, 741 F.3d 1314 (D.C. Cir. 2014)
- *U.S. v. US Stem Cell Inc. et al.*, No. 18-cv-61047 (S.D. Fla.) (J. Ungaro);
U.S. v. US Stem Cell Inc. et al., No. 19-13276 (11 Cir.)
- *U.S. v. Cell Surgical Network/California Stem Cell Treatment Centers et al.*, No. 18-cv-1005 (C.D. Cal.) (J. Bernal)

- **Seizure Pursuant to 21 U.S.C. § 334**

- *United States v. Five Articles of Drug, ACAM 2000, Vaccinia Virus Vaccine, Live*, No. 17-11448 (C.D. Cal. Mar. 20, 2018)



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351 CGT Products: Compliance Challenges

- Regulatory pathway (361 vs. 351) is a threshold question for HCT/P manufacturers (stem cell clinics)
- However, many cell and gene therapy products clearly fall into 351 and sponsors are not arguing otherwise (IND, BLA, GCP/GMP, etc.)
 - CAR-T cell products
 - CRISPR-Cas9 technology
 - Gene therapies
 - 800 CGT INDS submitted to FDA according to Dr. Marks
- Still face considerable compliance challenges
 - Clinical holds
 - Data integrity concerns
 - Manufacturing issues

Clinical Holds

- *21 CFR 312.42. Clinical holds and requests for modifications.*
 - **Clinical hold:** an order by FDA to delay a proposed clinical investigation, or suspend (fully or partially) an ongoing clinical study
 - Hold may be imposed for any of the reasons stated in 312.42(b), including “unreasonable and significant risk of illness or injury”
- At least 4 clinical holds for cell or gene therapy products just in the last 6 months
 - Likely more, but holds not always public (confidential unless disclosed by sponsor)
- All appear to be imposed under grounds of “unreasonable and significant risk of illness or injury”
- CGTs pose unique safety concerns + heightened sensitivity to safety issues (Jesse Gelsinger)
 - Viral vector associated toxicities
 - Cytokine release syndrome
 - Long-term consequences from gene editing
- Regenxbio lawsuit
- Trend in clinical holds? How can companies avoid holds?

Manufacturing

- Many CGTs begin in academic laboratories unfamiliar with FDA
 - Did lab follow GLPs and GCPs?
 - Is clinical data ALCOA such that it can be relied upon in a marketing application?
- Scale up from research to commercial manufacturing can be difficult
 - Unique issues with CGT products
 - Complex and individualized manufacturing
 - Often for rare diseases with limited patient population
 - How do GMPs apply?
 - Qualifying “API” (starting materials is often cells from individual patients, not “bulk” API)
 - Limited material available for lot release testing
 - Comparability and characterizing the product
 - Product tracking and segregation
 - Sterility, shipping, and storage concerns
 - How are processes validated and applied uniformly?
- Enzyvant Complete Response Letter for RVT-802 (congenital athymia) cited “manufacturing concerns”
- How will FDA and industry address manufacturing challenges?

Data Integrity

- Approval of Zolgensma for SMA (May 24, 2019)
- Data integrity concerns uncovered (June/July 2019)
 - Novartis informs FDA of data manipulation related to potency assay (June 28, 2019)
 - Avexis aware of the concern as early as January 2018 when it opened an NCR
 - Novartis opened second NCR in August 2018
 - FDA follows up with several review team meetings, inspection of Avexis facility (5 item 483), CBER Incident Review Memo
 - Novartis defends delayed notification to FDA
- Peter Marks statement (August 2019):
 - Totality of evidence supports safety and efficacy of product, it will remain on the market, but
 - FDA will pursue all appropriate civil and criminal penalties
- Dr. Sharpless speech to ResearchAmerica! (September 2019):
 - Stresses importance of data integrity in clinical trials, and that FDA will pursue civil and criminal penalties for data fraud
- Will FDA enforce against Novartis?

Final Thoughts

- Unique concerns with CGT products
 - Individualized and complex
 - Toxicity and other safety issues
 - Innovative technology (novel issues for FDA and industry)
 - Large volume of products; resource constraints at FDA
- Avoid compounding potential problems by proactively raising issues with FDA early
 - INTERACT Meetings
 - CATT
 - Pre-IND meetings/correspondence
 - ALWAYS timely report any data integrity concerns
- Due diligence is critical before a CGT product acquisition
- Fast paced environment
 - Expect change, and pay attention to FDA activity (guidances, WLs, holds, etc.)



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Avoiding Enforcement Action

- FDA Assistance on Product Classification and Jurisdiction
 - Tissue Reference Group (TRG) Rapid Inquiry Program (TRIP)
 - Program announced June 12, 2019 to help manufacturers of human cell, tissue, and cellular and tissue-based products- including stem cell treatments- understand the appropriate regulatory pathways for their products
 - Temporary program to quickly obtain an informal, non-binding assessment from FDA on how products are regulated
 - Recommendation regarding application of the criteria in 21 CFR 1271.10(a) to an HCT/P for a given indication for use

Avoiding Enforcement Action

- FDA Assistance on Product Classification and Jurisdiction
 - Pre-Request for Designation (pre-RFD)
 - Guidance for Industry- February 2018
 - Provides informal, non-binding feedback regarding the regulatory identity or classification of a human medicinal product as a drug, device, biological product, or combination product
 - Product assignment to appropriate Agency center (CDER, CDRH, or CBER)
 - Through Office of Combination Products (OCP)
 - Feedback within sixty (60) calendar days
 - Helps guide decision making (PD) by sponsor

Avoiding Enforcement Action

- FDA Assistance on Product Classification and Jurisdiction
 - Request for Designation (RFD)
 - FDA's formal response to an RFD and is a binding determination with respect to classification and/or center assignment
 - Useful when classification or assignment is unclear or in dispute
 - Response within sixty (60) calendar days

Avoiding Enforcement Action

- Third Party Assistance on Compliance and Regulatory Strategy
 - GTP/GMP Gap Assessment
 - Identifies noncompliance to FDA regulations
 - Provides recommended corrective actions to ensure compliance
 - Nonbiased, thorough review of QMS
 - Professional and/or legal interpretation of FDA regulation(s) and Guidance for Industry document(s)
 - Professional and/or legal guidance on product development and design changes
 - Regulatory pathway determination and strategy
 - 361 vs. 351
 - » 351- IND/BLA

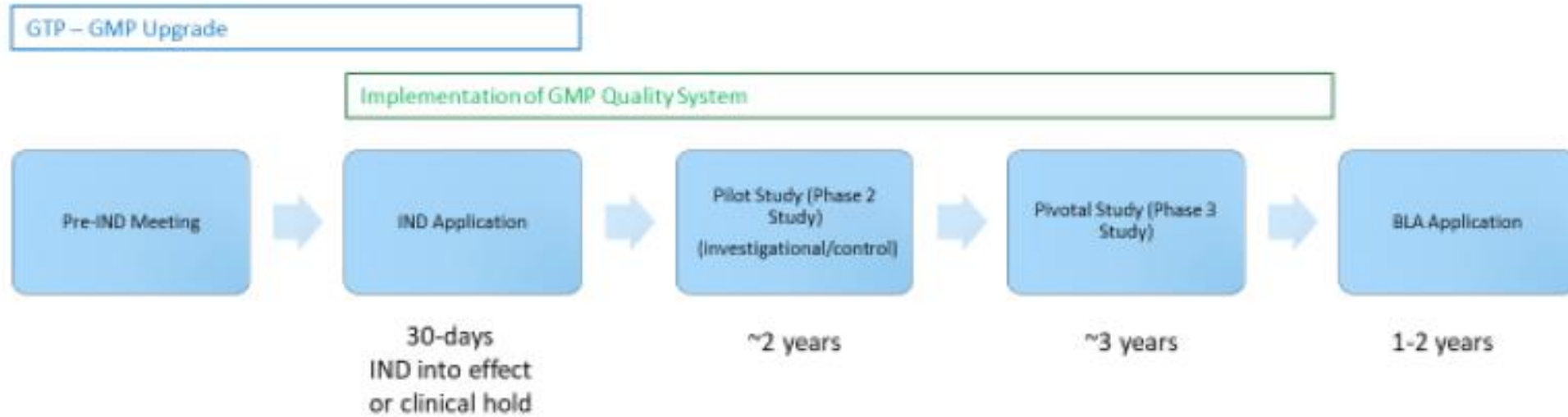
Addressing Enforcement Action

- Commitment to Appropriate Pre-Market Submission
 - Pre-Investigational New Drug Application (Pre-IND) Consultation Program
 - Program through CDER
 - Fosters early communications between sponsors and new drug review divisions to provide guidance on the data necessary to warrant IND submission
 - Investigational New Drug Application (IND)
 - Application to begin drug product use with clinical investigators
 - Early stages- Analysis for safety and pharmacological effect

Addressing Enforcement Action

- **Biologics License Application (BLA)**
 - Pre-market application with CBER for a biological product
 - Includes Pre-clinical and Clinical studies

IND/BLA Process



Addressing Enforcement Action

- Swift and thorough response to FDA
 - Emphasis on systemic corrective action
 - Professional assistance on containment, root cause analysis and CAPA assignment
 - Communication with the Agency
 - CBER
 - Local district office



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