Human Cellular and Tissue-Based Products (HCT/P), Cell Therapy and Gene Therapy

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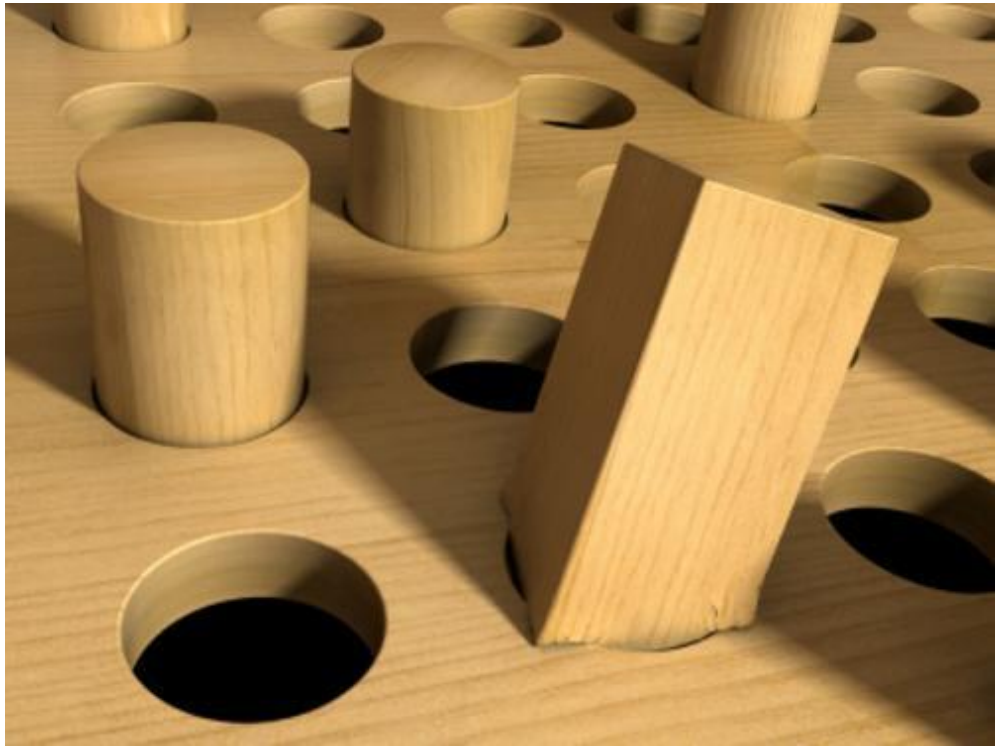
FDLI

Agenda

- Overview
- Regulation of HCT/Ps
- Cell Therapies/RMAT
- Regulation of Gene Therapy
- Key Points

What do HCT/Ps, Cell Therapies, and Gene Therapy have in common?



Early History of Transplantation in the US

- 1869 First successful recorded skin graft
- Early 1900s – scientists begin to understand basic immunology of transplantation
- First tissue bank created in 1949
  - U.S. Navy Tissue Bank
    - First national tissue processing and storage facility
    - Established many of the techniques and standards used in tissue banking today
- Rejection of allogeneic (non-self) tissue remained a significant barrier
- 1970s saw rapid development of transplant medicine
  - Discovery of cyclosporine's immunosuppressive effect
  - Legal changes supported organ and tissue donation (UAGA, brain death)

Early History of Transplantation in the US

- Organ and tissue transplantation clearly were considered part of the practice of medicine
- No consideration of FDA oversight
- Things began to change in the early 1990s ….

FDA Begins to Regulate Human Tissue

- Early 1990s: CDC reports disease transmission through human tissue transplantation
  - Unsafe tissue imported to U.S.
- FDA Commissioner orders investigation and identifies immediate need to protect the public health from transmission of infectious diseases (HIV, Hepatitis B, C)
- 1993: FDA issues Interim Final Rule

FDA Begins to Regulate Human Tissue

- What statutory authority could FDA cite to support jurisdiction?
  - Does human tissue meet the definition of a
    - Drug?
    - Device?
    - Biological product?
  - Is tissue “intended” by its manufacturer for use to diagnose, treat, mitigate, cure, or prevent disease?
  - Who would be the “manufacturer” for FDA regulatory purposes?

Human Tissue: FDA Jurisdiction?

- The Public Health Service Act
  - Enacted in 1944
  - Established federal government's quarantine authority
  - Gave authority to the Public Health Service (different agency under HHS) to prevent the introduction, transmission and spread of communicable diseases from foreign countries into the U.S.
- PHS Act Section 361 (42 USC 264):
  - *"The Surgeon General, with the approval of the Secretary, is authorized to make and enforce such regulations as in his judgment are necessary to prevent the introduction, transmission, or spread of communicable diseases from foreign countries into the States or possessions, or from one State or possession into any other State or possession. . . ."*

Human Tissue: FDA Jurisdiction?

- FDA had previously relied on PHS Act authority to regulate, among other things, source and use of potable water, milk pasteurization, and to prevent transmission of disease through animals (bird, shellfish, turtles etc.)
- State of La. v. Matthews, 427 F. Supp. 174 (1977)
  - Upheld FDA authority to ban intrastate sales of small turtles because of Salmonella risk
  - *"Congress has granted broad, flexible powers to federal health authorities who must use their judgment in attempting to protect the public against the spread of communicable disease."*

Interim Final Rule

- **Final:**
  - Immediately in effect (no proposed rule) FDA cites *"imminent need to protect the public health"*
- **Interim:**
  - Limited in scope
    - Acknowledges voluntary U.S. accreditation programs (AATB, EBAA)
    - Cites need for federal, enforceable standards to address risks of tissue sourced OUS
  - Limited in duration
    - *not intended to serve as a long term regulatory program for assuring the safety or quality of human tissues used in transportation,*
      - *In the near future, FDA **intends to propose more extensive regulations regarding infectious disease control** for tissues that would incorporate, but not be limited to, the elements described in this interim rule*

Interim Final Rule

- 21 CFR Part 1270
  - Applies to any "establishment or person" involved in "recovery, processing, storage, or distribution" of "banked human tissues"
    - "banked human tissue" = *"any tissue derived from a human body, which: (1) Is intended for administration to another human for the diagnosis,' cure, mitigation, treatment, or prevention of any condition or disease; (2) Is recovered, processed, stored, or distributed by methods not intended to change tissue function or characteristics*
      - Excludes kidney, liver, heart, lung, pancreas, or any other vascularized human organ;
      - Excludes semen or other reproductive tissues, human milk, and bone marrow.
      - Excludes products already being regulated as human drug, biological product, or medical device
        - » FDA history of ad hoc regulation of specific tissues
          - Corneal lenticules, dura mater, heart valves (devices)

Interim Final Rule

- Requires donor testing and screening for HIV, Hepatitis B and C, in accordance with written procedures
- Record keeping
- FDA inspection
- Recall and destruction of violative tissue
- Enforcement
  - PHS Act Section 368 (42 U.S.C. 271): violations of Section 361 punishable with imprisonment up to one year; up to $100,000 (if no death resulted) or $250,000 (if death resulted).
  - Federal courts have jurisdiction to issue injunctions against individuals or entities violating regulations issued per Section 361

From Human Tissue to HCT/P

- Final rule establishing 21 CFR 1270 published in July 1997
- Concurrently, FDA expanded focus beyond protecting public from disease transmission
- March 1997: “Proposed Approach to the Regulation of Cellular and Tissue-Based Products”
  - Conceptual framework (prefatory to proposed rule)
  - Tiered approach based on risk and need for FDA premarket review
  - Phased implementation
  - Meetings with key stakeholders to solicit feedback
  - Establishment of Tissue Reference Group within FDA
    - **What problem was FDA trying to solve?**

Human Cellular, Tissue, and Cellular and Tissue-Based Product

- *Articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient.*
  - *E.g., 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.*
  - NOT included:
    - Vascularized human organs for transplantation;
    - Whole blood or blood components or blood derivative products;
    - Secreted or extracted human products, such as milk, collagen, and cell factors;
    - Minimally manipulated bone marrow for homologous use
    - Etc.
  - Exceptions
    - Same surgical procedure, same individual
    - Recovery of reproductive cells/tissues for immediate transfer into partner

HCT/P: Rationale for Regulation

- Comprehensive system applicable to all HCT/Ps
- Increase safety and public confidence
- Promote research, development, or the availability of new products.
- Risk-based, to enable more effective use of agency resources
- Increase consistency and efficiency of agency decisionmaking

HCT/P: 3 Phases

(1) Registration and listing (Jan. 19, 2001)

(2) Donor screening criteria (May 25, 2004)

(3) Current Good Tissue Practice (Nov. 24, 2004)

HCT/P Differentiation

"361" HCT/Ps

- Minimal Manipulation
- Homologous Use
- Not Combined With Another Article
- No systemic effect (except autologous, family-related, or reproductive use)
- Regulated solely under PHSA 361
- Subject only to 21 CFR Part 1271

Other HCT/Ps

- Do not meet criteria for regulation solely under PHS Act 361
- May be regulated as drugs, devices, and/or biological products
  - Section 351 of PHS Act
  - FD&C Act
- Premarket authorization
- Demonstration of safety and effectiveness

HCT/P Differentiation

- 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;
  - For cells or nonstructural tissues, **processing that does not alter the relevant biological characteristics** of cells or tissues.
- Homologous Use
  - 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

The devil in the definitions ….

Guidance and More Guidance

- 2006: Minimal Manipulation of Structural Tissue (Jurisdictional Update); Guidance for Industry and FDA Staff (Sept. 2006) (superseded Nov. 2017)
- 2014: Minimal Manipulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps); Draft Guidance for Industry and Food Administration Staff" (Dec. 2014) (finalized 2017)
- 2014: Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) from Adipose Tissue: Regulatory Considerations; Draft Guidance for Industry (Dec. 2014) (withdrawn 2017)
- 2015: Homologous Use of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps); Draft Guidance for Industry and FDA Staff (Oct. 2015)
- Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) from Adipose Tissue: Regulatory Considerations; Draft Guidance for Industry (Nov. 2017)

Enforcement Discretion

- 2017: Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use
  - FDA announced 36 months of enforcement discretion to allow manufacturers time to assess regulatory status and seek approval if necessary
  - Risk-based enforcement in the interim
- 2020: Reissued guidance and extended enforcement discretion to **May 2021**

The end of enforcement discretion

- FDA sent at least 14 letters and 24 untitled letters to HCT/P manufacturers and ~ 400 IHCTOA letters to health care providers, clinics and manufacturers. Products of concern included:
  - Umbilical cord/umbilical cord blood
  - Adipose cell-derived products
  - Therapeutic claims, e.g., Alzheimer, Crohns, diabetes, Parkinsons, lupus

  - *Despite all of the FDA's efforts to engage industry, there continues to be broad marketing of these unapproved products for the treatment or cure of a wide range of diseases or medical conditions. … These regenerative medicine products are not without risk and are often marketed by clinics as being safe and effective for the treatment of a wide range of diseases or conditions, even though they haven't been adequately studied in clinical trials. We've said previously and want to reiterate here – there is no room for manufacturers, clinics, or health care practitioners to place patients at risk through products that violate the law . . . . CBER Director Peter Marks, Apr. 2021*

HCT/P: Litigation

- *United States of America v. Regenerative Sciences, LLC, 741 F.3d 1314* (D.C. Cir. 2014)
  - Orthopedists developed and performed the Regenexx-C Procedure as a treatment for arthritis and other orthopedic conditions
    - Procedure involved extracting mesenchymal stem cells from patient's bone marrow or synovial fluid (autologous)
    - Cells cultured ex vivo, proliferated, mixed with antibiotic and reinjected at site of orthopedic injury
  - FDA sought to enjoin distribution; obtained court injunction

HCT/P Litigation

- Regenerative sciences challenged FDA's jurisdiction:
  - Not a Drug or Biologic
  - Practice of Medicine
  - Exemption under Part 1271
- District and Appellate courts both agreed with FDA
  - Both FDCA and PHSA give FDA broad authority
  - Product does not qualify for HCT/P exemption
  - "Product" not just the cells, but the "mixture"
    - Court finds "there is no doubt" that product qualifies as prescription drug

Revocation of Part 1270

- In transition from Human Tissue to HCT/P, all HCT/Ps recovered before May 25, 2005 continued to be subject to Part 1270 and certain elements of Part 1271 (general provisions, registration and listing)
- Final rule, Jan. 14, 2022 revokes 21 CFR Part 1270
- Explains regulations are obsolete; supplanted by Part 1271

FDA Regulation of Cell and Gene Therapy

- Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products (58 Fed. Reg. 53248 (Oct. 14, 1993))
  - "statement" of how FDA's "current statutory authorities governing therapeutic products apply to human somatic cell therapy products and gene therapy products"
  - Notes that as scientific knowledge evolves, agency's approach may also evolve
  - Cites FDCA and PHSA
  - PHSA Section 351(a), 42 USC 262(a) – gives authority to regulate biological products
    - *any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or its derivatives (or any other trivalent organic arsenic compouod), applicable to the prevention, treatment, or cure of diseases or injuries of man."*
    - Requires approval of biologics license application (BLA) as a condition of marketing

FDA Regulation of Cell and Gene Therapy

- Definitions
  - *Somatic cell therapy is the prevention, treatment, cure, diagnosis, or mitigation of disease or injuries in humans by the administration of autologous, allogeneic, or xenogeneic cells that have been manipulated or altered ex vivo. Manufacture of products for somatic cell therapy involves the ex vivo propagation, expansion, selection, or pharmacologic treatment of cells, or other alteration of their biological characteristics.*
  - *Gene therapy is a medical intervention based on modification of the genetic material of living cells. Cells may be modified ex vivo for subsequent administration or may be altered in vivo by gene therapy products given directly to the subject. When the genetic manipulation is performed ex vivo on cells that are then administered to the patient, this is also a type of somatic cell therapy. The genetic manipulation may be intended to prevent, treat, cure, diagnose, or mitigate disease or injuries in humans*

➢ **Is this Rulemaking?**

FDA Regulation of Cell and Gene Therapy

- 1990: FDA approves first gene therapy trial
  - 2 children with SCID – response moderate, limited
- Realizing promise of gene therapy seemed imminent
- However, many safety and efficacy questions remained
- Death of Jesse Gelsinger in 1999
  - Severe immune reaction to the viral vector
  - Resulted in clinical hold on research program after FDA identified protocol deviations, failure to follow regulations
  - FDA investigated dozens of other gene therapy trials
  - Led to closer scrutiny, more regulatory caution, for of gene therapy research
- Reports of patients who developed cancer as a result of the viral vector
- Need for safe and effective **vectors** was major barrier to progress

FDA Regulation of Cell and Gene Therapy

- What's a vector?
  - Vehicle for delivery of therapeutic genetic material (e.g., a gene) directly into cells
- What types of vectors are there?
  - Viral – viruses are very good and getting into cells
    - Use viral machinery as "envelope" to deliver gene "message" to the cells
      - Limitations: adverse reaction, off-target effect, antibody response
  - Non-viral – deliver genetic material to cell through chemical or physical means
    - Liquid nanoparticle, electroporation
    - Not as far along in development

FDA Regulation of Cell and Gene Therapy

- Development of new delivery strategies (viral and non-viral) allowed field to advance
- 2017: FDA approves first gene therapy products
    - Luxterna – first directly administered gene therapy that targets a disease caused by mutations in a specific gene
    - Kymriah and Yescarta (CAR-T) – genetically alters patients cells ex vivo and reintroduces to attack cancer cells
- 2020: FDA issued six gene therapy-specific guidance documents describing expectations for research and development of new gene therapy products
- FDA receiving hundreds of investigational new drug (IND) applications for gene therapy products each year (354 in 2020)
  – backlog of more than 1,142 active cell therapy INDs and 1,201 active gene cell therapy INDs awaiting review
- On the horizon …. Gene editing
  – 2021 – FDA approves trial using CRSPR Cas9 to correct mutation causing sickle cell anemia

Regnerative Medicine Advanced Therapy (RMAT) Designation

- 21st Century Cures Act (2016): a drug is eligible for RMAT designation if:
  - is a regenerative medicine therapy
    - defined as a *cell therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product using such therapies or products, except for those regulated solely under Section 361 of the Public Health Service Act and part 1271 of Title 21, Code of Federal Regulations*
  - is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition; and
  - preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition
- Benefits similar to "breakthrough designation" (available for drugs and biological products)
- Unlike BTD, does not require evidence that the product offers substantial improvement over other therapies
  - Expedited and streamlined review process; early interaction to discuss use of surrogate or intermediate endpoints
  - FDA has received ~ 180 requests and granted ~ 67 overall

What do HCT/Ps, Cell Therapies, and Gene Therapy have in common? What are some differences