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HCT/P Regulation - 351 vs 361 Products

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Presentation Overview

- Introduction
- Public Health Service Act
- Regulation of HCT/Ps under Section 361 of the PHSA
- Regulation of Biologics under Section 351 of the PHSA
- Comparison between 351/361 Regulatory Pathways to Market

Introduction

- Sections 351 and 361 of the Public Health Service Act (PHSA) provides the authority for FDA to establish regulatory requirements for marketing traditional biologics and human cells, tissues, and cellular and tissue-based products (HCT/Ps). As discussed below, these two pathways differ markedly in terms of the time, effort and expense required to bring these products to market in the U.S.
- This presentation provides an overview of these regulatory requirements for marketing in the U.S. and discusses the differences in 351/361 regulatory requirements as well as any notable marketing restrictions associated with each pathway to market.

Historical Backdrop for the PHSA

- Prior to 1902, vaccines and biologicals were virtually unregulated in the U.S. Following the deaths of children infected with tetanus from a diptheria anti-toxin treatment, Congress passed the Biologics Control Act of 1902. The BCA required manufacturers of biologicals (vaccines) to meet established purity and safety guidelines. No specific statutory requirement for potency or efficacy.
- FDA read potency and efficacy into the statute by requiring that the products bear expiration dating.
- In 1944 Congress recodified the BCA into the PHSA and specifically added the requirement of potency as a measure of clinical utility. The administration of the PHSA was primarily given to the NIH but later transferred to FDA.
- Once FDA assumed regulation of biologicals, it applied the FDCA misbranding provisions applicable to drugs and thus required all new biologicals to satisfy the safety and efficacy standards as new drugs.

PHSA - Overview

- The PHSA established the federal government biologic quarantine authority for the first time, which gave the Public Health Service responsibility for preventing the introduction, transmission and spread of communicable diseases from foreign countries into the United States.
- Due to growing instances of the transmission of HIV through transplantation of human tissue in the early 1990s, FDA became acutely conscious of the need for increased federal regulation of tissue for transplantation to protect the public health from the transmission of disease – FDA turned to Section 361 of the PHSA to address these concerns.

PHSA – Sections 351 and 361

- **Section 351 of the PHSA identifies a set of products that will be regulated as biologicals.**
- **A biological product is a "virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, … applicable to the prevention, treatment, or cure of a disease or condition of human beings."**
  - These include blood-derived products, vaccines, in vivo diagnostic allergenic products, immunoglobulin products, products containing cells or microorganisms, and most protein products.
- **Section 361 of the PHSA does not identify a specific class of products. Rather, it gives FDA the authority to make and enforce such regulations that are necessary to prevent the introduction, transmission, or spread of communicable diseases from foreign countries into the States**

FDA Publication of 21 CFR 1270

- In 1993, pursuant to Section 361, FDA published an interim rule concerning human tissue intended for transplantation, which required testing for certain communicable diseases, along with donor screening, and record-keeping. 58 Fed. Reg. 65514 (December 14, 1993).
- FDA then issued a final rule entitled, "Human Tissue Intended for Transplantation" on July 29, 1997 creating Part 21 CFR 1270, which requires certain infectious disease testing , donor screening, and recordkeeping to help prevent the transmission of HIV and hepatitis viruses through human tissue used in transplantation.

FDA Publication of 21 CFR 1271

- **In 1997 FDA announced it plans for a more comprehensive system of regulation for HCT/Ps. The Agency's proposed approach was explained in two documents:**
  - "A Proposed Approach to the Regulation of Cellular and Tissue-Based Products," 62 Fed. Reg. 9721 (March 4, 1997)
  - "Reinventing the Regulation of Human Tissue."
- **Since 1997, FDA has published three final rules to implement various aspects of its "proposed approach." The first of these final rules was published in 2001 and created 21 C.F.R. Part 1271**

FDA Publication of 21 CFR Part 1271

- **Subpart A of Part 1271 contains definitions and general provisions pertaining to the scope and purpose of the HCT/P regulations. In particular, § 1271.10(a) sets out the criteria that form the foundation of a tiered, risk-based approach to regulating HCT/Ps.**
  - *Human cells, tissues, or cellular or tissue-based products (HCT/Ps)* means articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient.
- **Under this tiered approach, human tissue products that meet the defined criteria provided in 21 CFR Part 1271.10 are regulated solely under Section 361 of the PHSA.**

Criteria for Regulation as a Section 361 HCT/P

- **An HCT/P is regulated solely under Sec. 361 of the PHSA if it meets all of the following criteria:**
  - The HCT/P is minimally manipulated;
  - The HCT/P is intended for homologous use only;
  - The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage; and either:
  - (i) the HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or (ii) the HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and (a) is for autologous use; (b) is for allogeneic use in a first-degree or second-degree blood relative; or (c) is for reproductive use.

Examples of HCT/P's Regulated Solely under Section 361

Bone (incl. demineralized bone)	Ligaments
Tendons	Fascia
Cartilage	Ocular tissue
Skin	Veins and arteries (not from preserved umbilical cords)
Pericardium	Amniotic membrane (for ocular repair)
Dura matter	Heart valve allografts
Hematopoietic stem cells derived from peripheral or umbilical cord blood	Reproductive Cells (Semen, Oocytes)
Embryos	

Biologics Regulated under Section 351 of the PHS Act and/or the FD&C Act

- **Examples of products FDA has determined do not meet all of the criteria in 21 CFR 1271.10(a) and are regulated as drugs and/or biological products:**
  - CULTURED CARTILAGE CELLS
  - CULTURED NERVE CELLS
  - LYMPHOCYTE IMMUNE THERAPY
  - GENE THERAPY PRODUCTS
  - HUMAN CLONING
  - HUMAN CELLS USED IN THERAPY INVOLVING THE TRANSFER OF GENETIC MATERIAL (cell nuclei, oocyte nuclei, mitochondrial genetic material in ooplasm, genetic material contained in a genetic vector)
  - UNRELATED ALLOGENEIC HEMATOPOIETIC STEM CELLS
  - UNRELATED DONOR LYPHOCYTES FOR INFUSION

Important Definition: Minimum manipulation

***Minimal manipulation* means:**

(1) 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; and

(2) For cells or nonstructural tissues, processing that does not alter the relevant biological characteristics of cells or tissues.

21 CFR 1271.3

Key Definitions: Homologous Use/ Autologous 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 or functions in the recipient as in the donor.**
- ***Autologous use*** **means the implantation, transplantation, infusion, or transfer of human cells or tissue back into the individual from whom the cells or tissue were recovered.**

21 CFR 1271.3

Key Definitions – Not defined

- FDA has not yet promulgated regulatory definitions for the terms, “systemic effect” and “metabolic activity”, which are used in describing the criteria established at 21 CFR § 1271.10 for determining whether an HCT/P is regulated solely under 361.
- Thus, the lack of clarity about what “systemic effect” and “metabolic activity” means in the context of FDA’s HCT/P regulatory criteria leaves it open to interpretation.

Regulation of HCT/Ps Under Section 361

- HCT/Ps that are marketed under Section 361 are not required to obtain premarket approval/clearance from FDA. Distributors and marketers of HCT/Ps are permitted to self-designate the tissue products as meeting the criteria set forth under 21 CFR Part 1271.
- Although this regulatory framework is appropriate for traditional allograft products that are not intended for use as cell-based therapies, many other human tissue products entering the market cannot be considered lawful 361 HCT/Ps because they do not meet the regulation's four-part test for marketing under this provision noted below.
- Products that do not meet the four-part test require premarket approval/clearance before they may legally be marketed.

Part 1271 Regulatory Requirements

- **Domestic or foreign establishments that manufacture an HCT/P must comply with the following regulatory requirements:**
  - You must register your establishment with FDA;
  - You must submit to FDA a list of each HCT/P manufactured; and
  - You must comply with any other applicable requirements set forth in 21 CFR 1271.

Part 1271 Regulatory Requirements

- **As noted above, 21 CFR 1270 and 1271 require tissue establishments to screen and test donors, to prepare and follow written procedures for the prevention of the spread of communicable disease, and to maintain records.**
- **Tissue Establishment and Registration (Form FDA 3356) is required and must be updated annually**
- **Current Good Tissue Practices (cGTPs)**
  - 21 CFR part 1271.145-320 (Subpart D): quality program, personnel, procedures, facilities, environmental controls and monitoring, processing and controls, process changes, process validation, labeling controls, storage, supplies and reagents, equipment, recovery, records, tracking, complaints.

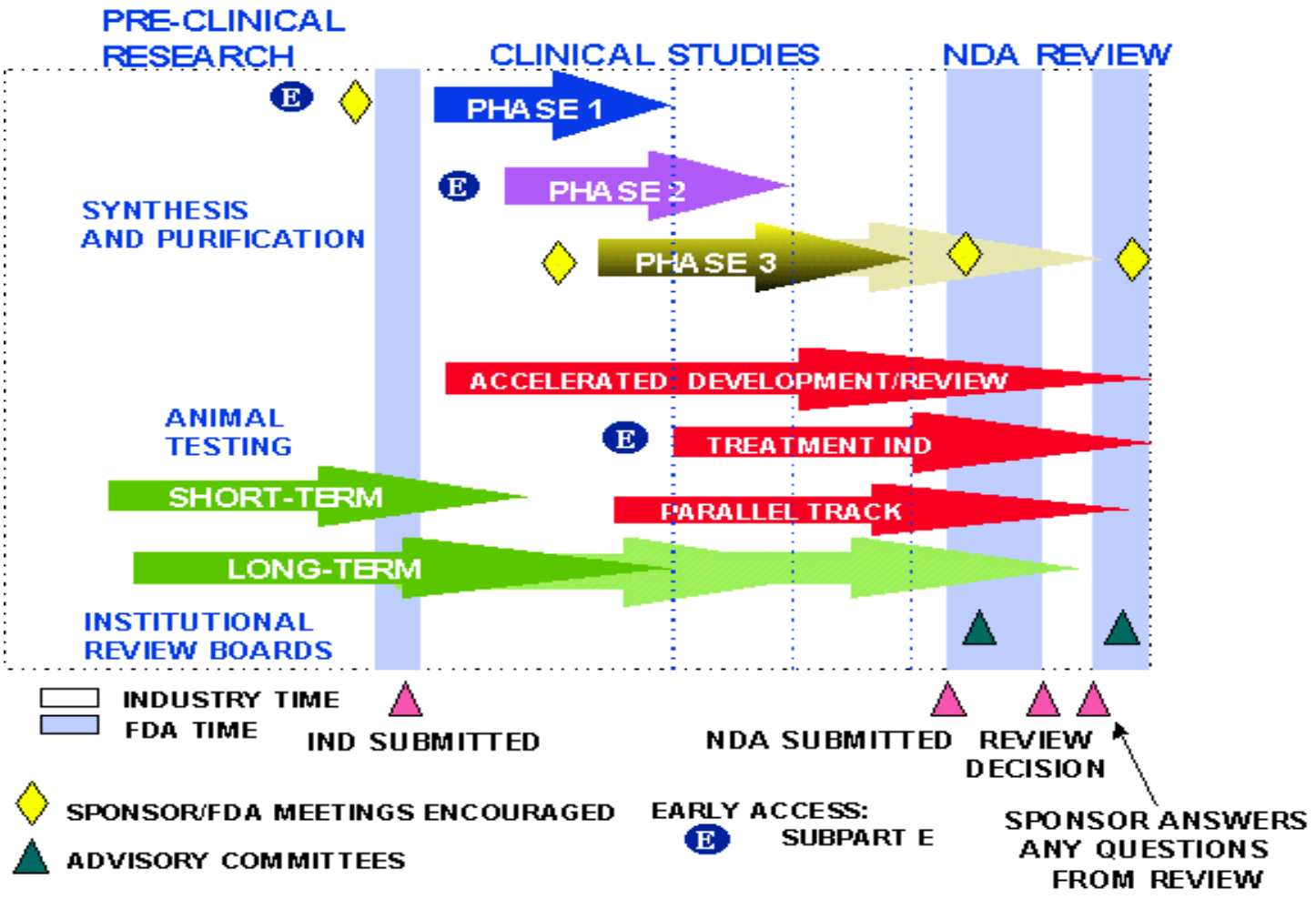
Tissue Reference Group

- To assist industry with determining the appropriate regulatory classification of an HCT/P, FDA established the Tissue Reference Group (TRG). The TRG is a multi-Center working group, that serves as a forum for making determinations about how a particular human tissue product will be regulated.
- In cases where the TRG determines that a product is not eligible for regulation solely under Part 361, the Office of Combination Products (OCP) is also involved in regulatory pathway decisions, determining which of FDA's Centers will have jurisdiction based on the product's primary mode of action through the Request for Designation process.

Biologics Regulated Under Sec. 351 of the PHSA

- Biologics that do not meet FDA's criteria for being regulated as an HTC/P under 361 are regulated by FDA under Sec 351 of the PHSA, which requires FDA approval of a Biologics License Application (BLA) for permission to introduce, or deliver for introduction, a biologic product into interstate commerce.
- A BLA can be submitted by any legal person or entity who is engaged in manufacture or an applicant for a license who takes responsibility for compliance with product and establishment standards. A completed Form FDA 356h must be submitted to FDA along with the required regulatory information outlined in the application.
- Biologics subject to the PHS Act also meet the definition of drugs under the Food Drug and Cosmetic Act

BLA Approval Process



Biologics – IND Requirements

- **An Investigational New Drug Application (IND) is a request for authorization from the Food and Drug Administration (FDA) to administer an investigational drug or biological product to humans. Such authorization must be secured prior to interstate shipment and administration of any new drug or biological product that is not the subject of an approved NDA or BLA. IND Application contents include, in part, the following:**
  - Cover Sheet – Form FDA 1571
  - Applicant information
  - Introductory Statement and Investigational Plan
  - Investigator's Brochure
  - Study Protocol
  - Chemistry, Manufacturing and Control information
  - Information about the biologic/product
  - IRB information
  - Clinical investigator CVs
  - Pharmacology/toxicology information
  - Previous human experience
  - Labeling

BLA – Application Requirements

- **In general, a BLA submission should include the following:**
  - Application Form FDA 356h
  - Summary of the Application
  - Chemistry, Manufacturing and Control information Product Description
  - Environmental impact
  - Nonclinical pharmacology/toxicology
  - Human pharmacokinetics/bioavailability
  - Microbiology
  - Clinical data section
  - Statistical section
  - Pediatric use section
  - Draft Labeling
  - Case report forms and tabulations
  - Patient information

Biologics – Approval Process

- If the data generated by the studies demonstrate that the product is safe and effective for its intended use, the data are submitted as part of a BLA marketing application.

- FDA form 356h is used for both NDA and BLA submissions. FDA approval to market a biologic is granted by issuance of a biologics license.

- Issuance of a biologics license is a determination that the product, the manufacturing process, and the manufacturing facilities meet applicable requirements to ensure the continued safety, purity and potency of the product.

BPCI Act of 2009

Biologics Price Competition and Innovation Act of 2009:

- Signed into law March 23, 2010
- Intent of the statute similar to Hatch-Waxman Amendments to FD&C Act
- Aligns with the FDA's longstanding policy of permitting appropriate reliance on what is already known about a drug, thereby saving time and resources and avoiding unnecessary duplication of human or animal testing.
- Balances additional incentives to innovate and price competition
- Created abbreviated approval pathway for follow-on biologics.

Biologics – Post Marketing Requirements

- FDA continues to assure product safety and efficacy after a product is approved. These post-market activities include lot release (for some products), post-marketing adverse event reporting, and post-marketing study commitments (also known as Phase IV studies).

Comparison – 351/361 Requirements

Section 351 Biologic	HCT/Ps – 361
➢ BLA application requires submission of bench, animal human data and other information to establish product safety and efficacy	➢ Self- designate as compliant with 21 CFR 1271
➢ Time to market from first development: 10+ yrs.	➢ Time to Market: 1-2+ yrs.
➢ Develop. Costs: $$$ Millions	➢ Develop. Costs: ~ $1 mil. or more
➢ User fees: Application fee w/ clinical data: $2,038,100; Establishment Reg. Fee (annual): $512,200; Product Fee (annual): $97,750	➢ Application fee: None

FDA Draft HCT/P Guidance

- **FDA issued the following HCT/P guidance documents in 2014/2015 to help industry and FDA staff identify when a product should be regulated under 361 versus 351:**
  - "Minimal Manipulation of Human Cells, Tissues and Cellular and Tissue Based Products - Draft Guidance for Industry and FDA Staff" (December 2014); and
  - "Homologous Use of Human Cells, Tissues, and Cellular and Tissue-Based Products - Draft Guidance for Industry and FDA Staff" (October 2015).

Draft HCT/P Guidance

- **As of February 2017 FDA had not finalized the HCT/P guidance. In addition, it does not appear that FDA has been taking enforcement action related to HCT/P products on the market that don't fully comply with the criteria established by FDA to be regulated under 361.**

Regenerative Medicine and 21st Century Cures

- **Gives FDA the authority to grant accelerated approval for regenerative medicines, allows certain regenerative medicine products to be designated as a "regenerative advanced therapy" and become eligible for priority review by FDA.**
  - Defined as "cell therapy, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products, except for those regulated solely under section 361 of the Public Health Service Act."
- **Accelerated approval means that a sponsor can skip straight over efficacy testing in humans, to go directly to post-market review.**
- **Must address a serious disease and have the potential to deal with currently unmet medical needs.**

QUESTIONS?