FDA Regulatory, Compliance and Policy Developments: "361 HCT/Ps"

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What are "361 HCT/Ps"?

Examples include the following (if they comply with certain criteria)

- Bone (including demineralized bone)
- Tendons
- Ligaments
- Fascia
- Cartilage
- Skin
- Ocular Tissues
- Vascular grafts (veins and arteries)
- Pericardium
- Amniotic Membrane
- Dura Mater
- Heart Valve
- Allografts
- Hematopoietic Stem Cells
- Oocytes
- Semen
- Embryos

Definition of HCT/P

- ***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. 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. (21 C.F.R. 1271.3(d))

- Some exclusions

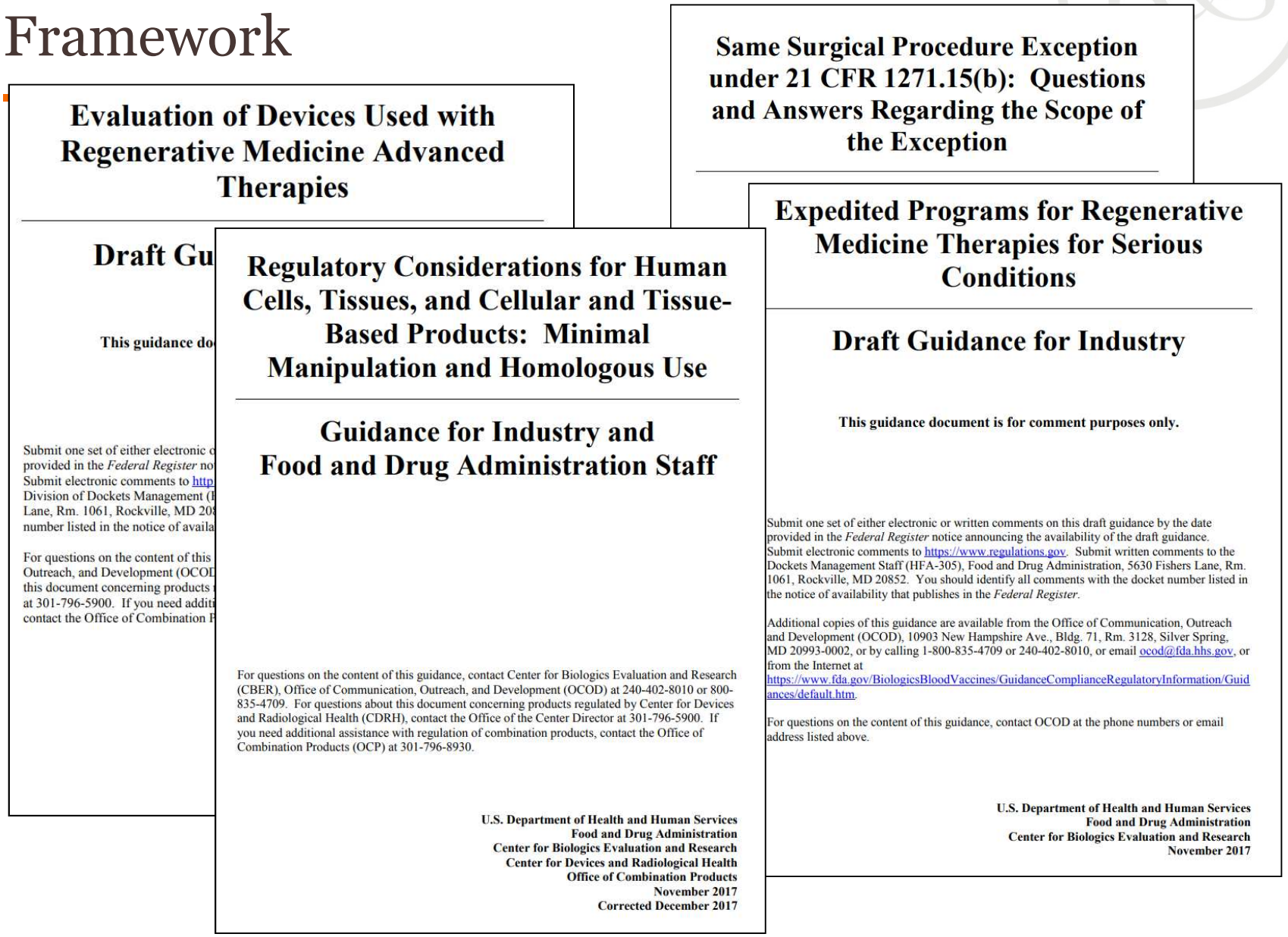
Regulatory Framework for HCT/Ps

- Some HCT/Ps are not regulated if they are removed from and implanted into the same individual during the same surgical procedure and remain in their original form ("**Same Surgical Procedure exemption**") (21 CFR 1271.15)

- Some HCT/Ps are regulated solely under 21 CFR Part 1271, issued under authority of section 361 of the Public Health Service Act (**"361 HCT/Ps"**).
  - Certain requirements (registration/listing, donor eligibility, Good Tissue Practices), but no premarket review

- Other HCT/Ps are subject to Part 1271 requirements and FDA requirements for medical devices, drugs, or biologics, including premarket review requirements.

Nov. 2017: Comprehensive Policy Framework



Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception

Evaluation of Devices Used with Regenerative Medicine Advanced Therapies

Draft Gu

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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

For questions on the content of this guidance, contact Center for Biologics Evaluation and Research (CBER), Office of Communication, Outreach, and Development (OCOD) at 240-402-8010 or 800-835-4709. For questions about this document concerning products regulated by Center for Devices and Radiological Health (CDRH), contact the Office of the Center Director at 301-796-5900. If you need additional assistance with regulation of combination products, contact the Office of Combination Products (OCP) at 301-796-8930.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Center for Devices and Radiological Health
Office of Combination Products
November 2017
Corrected December 2017

Expedited Programs for Regenerative Medicine Therapies for Serious Conditions

Draft Guidance for Industry

This guidance document is for comment purposes only.

Submit one set of either electronic or written comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-8010, or email ocod@fda.hhs.gov, or from the Internet at https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
November 2017

Criteria for Regulation as a 361 HCT/P

* Must be minimally manipulated
* Must be intended for homologous use only
- Must not be combined with other articles except water, crystalloids, or a sterilizing, preserving, or storage agent
- Must not have a systemic effect or be dependent upon the metabolic activity of living cells for its primary function (with certain exceptions).

See 21 C.F.R. 1271.10.

Minimal Manipulation

- Structural versus non-structural tissue
- 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 non-structural tissue or cells: “processing that does not alter the relevant biological characteristics of cells or tissues”

21 C.F.R. 1271.10(f); see also *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* (“**361 HCT/P Guidance**”).

Minimal Manipulation (cont'd)

Examples:

- Minimal manipulation of skin: mechanical meshing and cryopreservation. "The HCT/P generally is considered minimally manipulated because the processing does not alter the original relevant characteristics of the skin relating to its utility as a protective covering."

- More than minimal manipulation of amniotic membrane: grinding and lyophilization to create particles. "The HCT/P is generally considered more than minimally manipulated because the processing alters the original relevant characteristics of the HCT/P relating to its utility to serve as a barrier [physical integrity, tensile strength, and elasticity]."

See 361 HCT/P Guidance.

Minimal Manipulation (cont'd)

- Minimal manipulation of hematopoietic stem/progenitor cells: cell selection to obtain higher concentration for transplantation. "The HCT/P generally is considered minimally manipulated because the concentrated peripheral blood stem/progenitor cells are not altered with regard to their relevant biological characteristics to repopulate the bone marrow."
- More than minimal manipulation of cord blood product: cell selection and incubation with culture media and growth factors to achieve large numbers of cells capable of long-term repopulation of bone marrow. "This HCT/P derived from cord blood would generally be considered more than minimally manipulated because the processing affects the production of intracellular or cell-surface proteins and other markers of cell lineage, activation state, and proliferation, thereby altering the cells' relevant biological characteristics of multipotency and capacity for self-renewal."

See 361 HCT/P Guidance.

Homologous Use

- Defined as “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.” (21 C.F.R. 1271.10(c))

Examples:

- Homologous use: “Adipose tissue…used to fill voids in the face or hands…is homologous use because providing cushioning and support, is a basic function of adipose tissue.”
- Homologous use: “An acellular dermal product…used for supplemental support, protection, reinforcement, or covering for a tendon…is homologous use because in both anatomic locations, the dermis provides support and protects the soft tissue structure from mechanical stress.”
- Non-homologous use: “An amniotic membrane product is used for wound healing and/or to reduce scarring and inflammation. This is not homologous use because wound healing and reduction of scarring and inflammation are not basic functions of amniotic membrane.”
- Non-homologous use: “[Hematopoietic stem/progenitor cells] from cord blood are intended … to treat cerebral palsy purportedly through the repair of damaged tissue in the brain through paracrine signaling or differentiation into neuronal cells. This is not homologous use because there is insufficient evidence to support that repair of neurologic tissue through paracrine signaling or differentiation into neuronal cells is a basic function of these cells in the donor.

See 361 HCT/P Guidance.

Getting Clarity Beyond FDA's Guidance

- Formal and informal feedback on the regulatory status of particular HCT/Ps is available through FDA:
  - Tissue Reference Group (TRG) (recommendations)
  - Office of Combination Products (Request for Designation (RFD) (formal) or Pre-RFD (informal))

361 HCT/P Compliance: Enforcement Discretion

- Current policy of enforcement discretion
  - 36 months running from November 2017
- Qualifying criteria: “use of the HCT/P does not raise reported safety concerns or potential significant safety concerns.”
- Purpose: “To give manufacturers time to determine if they need to submit an IND or marketing application… and, if such an application is needed, to prepare the IND or marketing application….”

361 HCT/P Guidance.

361 HCT/P Compliance: Enforcement Action

- January 3, 2018 Warning Letter to American CryoStem Corporation regarding adipose-derived stem cell product
- In press release, FDA affirmed that it "intends to apply a risk-based approach to enforcement…[and] does not intend to exercise…enforcement discretion for… products whose use poses a potential significant safety concern."

361 HCT/P Compliance: Enforcement Action

- FDA 's Warning Letter identified potential significant safety concerns based on:
  - Product's routes of administration (intravenous, intrathecal, by aerosol inhalation)
  - Product's promotion for treatment of serious or life-threatening diseases, including Parkinson's disease, amyotrophic lateral sclerosis (ALS), stroke, and multiple sclerosis (MS)
  - Deviations from current good manufacturing practice requirements in product manufacture that "pose a significant risk that [the product] may be contaminated with microorganisms or have other serious product quality defects…."
- Previous Warning Letters about other types of HCT/Ps have expressed similar concerns regarding potential safety risks.

Fostering HCT/P Innovation

- Though not a free pass for all non-361 HCT/Ps, FDA's general enforcement discretion policy seeks to facilitate growth and development in the industry.

- FDA's new framework also aims to spur innovation by:
  - Providing expedited programs for sponsors of regenerative medicine therapies, including the new Regenerative Medicine Advanced Therapy (RMAT) designation created by the 21st Century Cures Act
  - Simplifying application of regulatory requirements for devices used in recovery, isolation, or delivery of RMATs.

Fostering HCT/P Innovation (cont'd)

- RMAT designation available for products that:
  - Are regenerative medicine therapies (cell therapies, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products, but not including 361 HCT/Ps);
  - Are intended for a serious or life-threatening disease or condition; and
  - Are the subject of preliminary clinical evidence that indicates that the product has the potential to address unmet medical needs.

Fostering HCT/P Innovation (cont'd)

- RMAT-designated products are eligible for Breakthrough Therapy benefits, including early actions to expedite development and potential rolling and/or priority review, as well as potential accelerated approval based on surrogate or intermediate endpoints.

- At least 21 RMAT designations awarded to date (designations began in 2017).

Thank you! We'll now have discussion with our esteemed industry representatives.