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

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Glossary of Terms[1]

Accelerated Approval:[2] An **expedited program** designation available for a product that is intended to treat a **serious condition** based on: previously agreed-upon **surrogate** or **intermediate endpoints** that are reasonably likely to predict long-term clinical benefit; or reliance upon data obtained from a meaningful number of sites, including through expansion to additional sites, as appropriate. Accelerated approval has been used primarily in settings in which the disease course is long and an extended period of time would be required to measure the intended clinical benefit of a drug.

Adipose Tissue:[3] Connective tissue composed of clusters of cells (adipocytes) surrounded by a reticular fiber network and interspersed small blood vessels, divided into lobes and lobules by connective tissue septa. Additionally, adipose tissue contains other cells, including preadipocytes, fibroblasts, vascular endothelial cells, and macrophages. Adipose tissue provides cushioning and support for other tissues, including the skin and internal organs, stores energy in the form of lipids, and insulates the body.

Allogeneic Therapy:[4] Use of human cells or tissue that is not **autologous**, i.e., not implanted transplanted, infused, or transferred back into the individual from whom the cells or tissue were recovered.

Autologous Use:[5] The implantation, transplantation, infusion, or transfer of human cells or tissue back into the individual from whom the cells or tissue were recovered.

Biological Product:[6] A virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound) applicable to the prevention, treatment, or cure of a disease or condition of human beings.

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[1] This document is intended for educational purposes only and does not constitute legal advice.
[2] 21 U.S.C. § 356(c).
[3] Guidance for Industry: Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use (July 2020) 9, available at https://www.fda.gov/media/109176/download [hereinafter Minimal Manipulation Guidance].
[4] 21 CFR 1271.65.
[5] 21 CFR 1271.3(a); Guidance for Industry: Same Surgical Procedures (November 2017) 5, available at https://www.fda.gov/media/89920/download [hereinafter Same Surgical Procedures Guidance].
[6] 42 U.S.C. §262(i)(1).

Breakthrough Therapy Designation:[7] An **expedited program** designation available for a product that is: intended to treat a **serious condition**, and for which preliminary clinical evidence indicates that the product may demonstrate substantial improvement over available therapies on one or more clinically significant endpoints.

Engineered Site-Specific Endonucleases:[8] Enzymes that are capable of precisely cleaving (cutting) DNA based on specific recognition of the DNA sequence at or near the site of DNA cleavage.

Expedited Programs:[9] Available for regenerative medicine therapies to treat, modify, reverse, or cure **serious conditions**. Expedited programs include **Regenerative Medicine Advanced Therapy Designation, Fast Track Designation, Breakthrough Therapy Designation, Accelerated Approval Designation, and Priority Review Designation**.

Fast Track Designation:[10] Available for an investigational new drug that is intended to treat a **serious condition**, and for which nonclinical or clinical data demonstrate the potential to address an **unmet medical need** in patients with such condition.

Genome Editing:[11] A process by which DNA sequences are added, deleted, or replaced at specified location(s) in the genome using site-specific nuclease-dependent or nuclease-independent technologies.

Gene Transfer:[12] The transfer of genetic material into a cell.

Homologous Use:[13] 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.

Human Cellular and Tissue-Based Products (HCT/Ps):[14] 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.

Human Gene Therapy Product:[15] Includes all products that mediate their effects by transcription or translation of transferred genetic material or by specifically altering host (human) genetic sequences. Some examples of gene therapy products include nucleic acids (e.g., plasmids, in vitro transcribed

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[7] 21 U.S.C. § 356(a).
[8] Guidance for Industry: Long Term Follow-Up After Administration of Human Gene Therapy Products (January 2020) 28, available at https://www.fda.gov/media/113768/download [hereinafter Long Term Follow Up Guidance].
[9] 21 U.S.C. § 356.
[10] 21 U.S.C. § 356(b).
[11] Long Term Follow Up Guidance, *supra* note 8, at 28.
[12] *Id.*
[13] 21 CFR 1271.3(c).
[14] 21 CFR 1271.3(d).
[15] Long Term Follow Up Guidance, *supra* note 8, at 28.

ribonucleic acid (RNA)), genetically modified microorganisms (e.g., viruses, bacteria, fungi), engineered site-specific nucleases used for human genome editing, and ex vivo genetically modified human cells.

Integration (of DNA):[16] The process whereby exogenous DNA sequences become incorporated into a genome.

Intermediate Endpoint:[17] When used in the context of **expedited programs**, a measurement of a therapeutic effect that can be measured earlier than an effect on irreversible morbidity and mortality (IMM) and is considered reasonably likely to predict the drug's effect on IMM or other clinical benefit.

Latency (of a viral infection):[18] A period of time during which a virus is present in the host without producing overt clinical symptoms.

Minimal Manipulation:[19] 1) For **structural tissues**, processing that does not alter the **original relevant characteristics** of the tissue relating to the tissue's utility for reconstruction, repair, or replacement; 2) For cells or nonstructural tissues, processing that does not alter **the relevant biological characteristics** of cells or tissues.

Original Relevant Characteristics:[20] When used in the context of **structural tissues**, generally includes the properties of that tissue in the donor that contribute to the tissue's function or functions.

Orphan Drug:[21] A drug that is intended for the treatment of a rare disease or condition (affects fewer than 200,000 persons in the United States), or for which there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the United States.

Persistence:[22] With respect to transferred or altered genetic material, the continued presence of transferred or modified genetic sequences in the host after acute exposure to a gene therapy agent, whether due to integration of the genetic sequence into the host genome, deletion, insertion, or otherwise modified following genome editing, or to latent infection with the viral vector bearing the genetic sequence.

Priority Review Designation:[23] An **expedited program** designation available for a product that treats a serious condition, and, if approved, would provide a significant improvement in the safety or effectiveness of the treatment of the condition.

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[16] *Id*.
[17] Guidance for Industry: Expedited Programs for Regenerative Medicine Therapies for Serious Conditions Guidance (February 2019) 4, available at https://www.fda.gov/media/120267/download [hereinafter Expedited Programs Guidance].
[18] Long Term Follow Up Guidance, *supra* note 8, at 28.
[19] 21 CFR 1271.3(f).
[20] Minimal Manipulation Guidance, *supra* note 3, at 7.
[21] 21 U.S.C. §360bb.
[22] Long Term Follow Up Guidance, *supra* note 8, at 28.
[23] Expedited Programs Guidance, *supra* note 17, at 9.

Reactivation (of a viral infection):[24] The re-emergence of a symptomatic or asymptomatic viral infection following a period of latency.

Regenerative Medicine Advanced Therapy (RMAT) Designation (also known as **Regenerative Advanced Therapy**):[25] An expedited program for **regenerative medicine therapies** that are intended to treat, modify, reverse, or cure a **serious condition**; and preliminary clinical evidence indicates that the regenerative medicine therapy has the potential to address **unmet medical needs** for such condition.

Regenerative Medicine Therapy:[26] 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 21 CFR part 1271. **Human gene therapy products** and xenogeneic cell products (products using non-human tissues or cells) may also meet the definition of a regenerative medicine therapy.

Relevant Biological Characteristics:[27] When used in the context of cells or nonstructural tissues, generally includes the properties of the cells or nonstructural tissues in the donor that contribute to the cells of tissue's function or functions. Examples of relevant biological characteristics of cells or nonstructural tissues include differentiation and activation state, proliferation potential, and metabolic activity.

Replication Competent Retrovirus (RCR):[28] A family of viruses that may potentially be generated during the manufacture of a retrovirus vector. At this time, the most common retrovirus-based vectors are constructed from gammaretroviruses or lentiviruses. The potential pathogenicity of RCR requires vigilant testing to exclude its presence in retroviral vector-based human gene therapy products.

Same Basic Function or Functions:[29] When used in the context of **homologous use**, those basic functions the **HCT/P** performs in the body of the donor (what the **HCT/P** does from a biological/physiological point of view, or is capable of doing when in its native state), which, when transplanted, implanted, infused, or transferred, the **HCT/P** would be expected to perform in the recipient. An **HCT/P** may perform the same basic function or functions even when it is not used in the same anatomic location where it existed in the donor.

Same Surgical Procedure Exception:[30] Procedures that involve an incision or instrumentation during which an **HCT/P** is removed from and implanted into the same individual within a single operation performed at the same establishment. Examples include autologous skin grafting, and coronary artery bypass surgery involving autologous vein or artery grafting.

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[24] Long Term Follow Up Guidance, *supra* note 8, at 28.
[25] 21 U.S.C. § 356(g).
[26] 21 U.S.C. § 356(g)(8).
[27] Minimal Manipulation Guidance, *supra* note 3, at 15.
[28] Guidance for Industry: Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up (January 2020) 1, available at https://www.fda.gov/media/113790/download.
[29] Minimal Manipulation Guidance, *supra* note 3, at 17.
[30] Same Surgical Procedures Guidance, supra note 5, at 5.

Serious Disease or Condition:[31] When used in the context of **expedited programs**, a disease or condition associated with morbidity that has a substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible if it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one. All conditions that meet the definition of life-threatening as set forth in 21 C.F.R. 312.81(a) would also be serious conditions.

Structural Tissues:[32] When used in the context of **minimal manipulation**, tissues that physically support or serve as a barrier or conduit, or connect, cover, or cushion in the donor are generally considered structural tissues for the purposes of determining the applicable regulatory definition. Examples of structural tissues include bone, skin, amniotic membrane and umbilical cord, blood vessel, **adipose tissue**, articular cartilage, non-articular cartilage, and tendon or ligament.

Surrogate Endpoint:[33] When used in the context of **expedited programs,** a marker such as a laboratory measurement, radiographic image, physical sign, or other measure, that is thought to predict clinical benefit, but is not itself a measure of clinical benefit.

Transgene:[34] An exogenous gene that is introduced into a host cell.

Unmet Medical Need:[35] When used in the context of **expedited programs,** a condition whose treatment or diagnosis is not addressed adequately by available therapy. An unmet medical need can be an immediate need for a defined population (i.e., to treat a serious condition with no or limited treatment) or a longer-term need for society (e.g., to address the development of resistance to antibacterial drugs).

Vector Sequences:[36] Specific sequences of nucleotides, either DNA or RNA, that have been introduced into a gene therapy product and includes the vector backbone, transgene(s), and regulatory elements.

Vector:[37] A vehicle consisting of, or derived from, biological material that is designed to deliver genetic material. Examples include plasmids, viruses, and bacteria that have been modified to transfer genetic material.

[31] Expedited Programs Guidance, *supra* note 17, at 3.
[32] Minimal Manipulation Guidance, *supra* note 3, at 8-9.
[33] Expedited Programs Guidance, *supra* note 17, at 4.
[34] Long Term Follow Up Guidance, *supra* note 8, at 29.
[35] Expedited Programs Guidance, *supra* note 17, at 3.
[36] Long Term Follow Up Guidance, *supra* note 8, at 29.
[37] *Id.*