FDA Regulation of Human Cells and Tissues

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This presentation will focus on human cells and tissues and details of the regulatory approaches for these products. To help you understand the regulatory approaches, this presentation will first provide a brief history of the regulatory approaches' development, and a description of the cells and tissues covered under Title 21 of the Code of Federal Regulations, or CFR, section 1271.

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In the early 1990's, the Centers for Disease Control and Prevention reported that HIV had been transmitted through transplantation of human tissue. There were also reports which suggested that potentially unsafe tissue for transplantation was being imported into the United States. The Commissioner of the FDA ordered an investigation and identified an immediate need to protect the public health from the transmission of diseases, particularly HIV and Hepatitis B and C, through transplantation of unsuitable tissue. This led to the publication of an interim final rule in December 1993 which was immediately implemented. The FDA promulgated this rule under the authority of the U.S. Public Health Service Act, specifically Section 361, which authorizes the creation and enforcement of regulations judged necessary to prevent the introduction, transmission, or spread of communicable diseases.

After a period of public comment, the final rule was issued in July 1997. This rule, called Part 1270, required certain communicable disease testing, donor screening, and record keeping for human tissue intended for transplantation. It was limited in scope, in that it only addressed donor screening and testing for tissues that were obtained from nonliving donors, specifically musculoskeletal tissue, ocular tissue, and skin.

That same year, 1997, FDA presented a consolidated regulatory approach that was more inclusive, covering all cells and all tissues, but at the same time was tiered and risk-based, to allow for less regulatory evaluation of products determined to be less risky. When FDA announced this approach, it explained this approach applied to human cells, tissues, and cellular or tissue-based products, referred to as HCT/Ps.

This announcement was followed by rulemaking with public and stakeholder feedback and, because of the complexity, was implemented in three separate parts or rules. It is now codified under 21 CFR section 1271, and became effective on May 25, 2005.

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21 CFR 1271 provides the basis for regulation of all HCT/Ps, and for some of these products, it is the sole regulatory requirement. Again, FDA regulates these products under the authority of Section 361 of the Public Health Service, or PHS, Act, which addresses prevention of the introduction, transmission, or spread of communicable disease. Products regulated solely under this authority do not undergo pre-market review. A broad range of tissue and cell products do meet the criteria for regulation solely under Section 361 of the PHS Act. This level of regulation is felt to be commensurate with the risk posed by the products.

HCT/Ps that do not meet the criteria to be regulated solely under Section 361 of the PHS Act are regulated as drugs, devices, and/or biological products. These are subject to the regulations specific to drugs, biological products, or medical devices. The tissue regulations in Part 1271 supplement these other requirements.

Applying the tiered, risk-based approach in this way, improper handling or processing that might contaminate or damage tissues can be prevented, while ensuring that clinical safety and effectiveness are demonstrated for more complex cells and tissues that are highly processed, used for purposes other than replacement of native tissues, combined with non-tissue components, or that have systemic effects.

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This slide shows a general list of the wide variety of cells and tissues that are considered to be HCT/Ps in accordance with the definition in the regulations. You can see that many HCT/Ps are from deceased donors, including the previously mentioned musculoskeletal, ocular, and skin tissues, as well as human heart valves and dura mater. There are also HCT/Ps from living donors, such as reproductive cells and tissues, and stem cell therapies.

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The products listed on this slide are specifically excluded from the definition of HCT/Ps. Most of these products fall under the jurisdiction of other parts of the FDA or the Department of Health and Human Services. For example, blood products are regulated by the FDA's Office of Blood Research and Review within CBER, and collagen and in vitro diagnostic products are regulated by the FDA's Center for Devices and Radiological Health. Vascularized organs and the blood vessels recovered with an organ, as well as minimally manipulated bone marrow from volunteer, unrelated donors are overseen by the Health Resources and Services Administration.

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Subpart A explains the scope and purpose of the regulation, and provides definitions of the terms used in the regulations. Subpart A also delineates the four criteria that a product must meet for it to be regulated solely under Section 361 of the PHS Act. Products are minimally manipulated or processed, perform

the same basic function in the recipient as in the donor, are not combined with another drug or device, and do not have a systemic or metabolic effect. A human cell, tissue, or cellular or tissue-based product that meets all four of these criteria is subject only to regulation under Section 361 of the PHS Act, and no premarket submission would be required. Subpart A also describes certain well-defined exceptions from the requirements.

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There are some definitions included in Subpart A that will be helpful explanations, in order for you to understand the regulations. HCT/Ps are defined to mean articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient.

Manufacture is defined as any or all steps in the recovery, processing, storage, labeling, packaging, or distribution of a human cell or tissue or in the screening or testing of cell or tissue donor. For example, infectious disease testing of samples of donor blood meets the definition of manufacture, because this is a step in testing a cell or tissue donor.

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Subpart B of Part 1271 addresses registration and listing. As part of rulemaking, it was determined that for the regulatory system to be effective in preventing the spread of disease, basic information about the HCT/P industry and its products must be obtained. This baseline data assists the agency in reacting swiftly to newly discovered risks and in conducting inspections. Therefore, establishments that manufacture an HCT/P must register and submit a list of every HCT/P that is manufactured in the establishment. This must be done within 5 days after beginning operations, and it must be updated at least annually.

It is important to emphasize that registration is not the same as a pre-market review, nor does it ensure compliance with all regulations. FDA determines compliance through periodic inspections. Registration provides the FDA with a list of establishments and products to inspect. Once an establishment registers, it can market and distribute its product without an inspection by the FDA.

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Foreign establishments that import HCT/Ps to the United States must also register. They must identify a U.S. agent who is located in the U.S. with an address and a phone number. The U.S. agent should assist with language differences and facilitate foreign inspections. The expectation is that all HCT/Ps distributed in the U.S. are manufactured in accordance with the U.S. FDA requirements.

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This is the registration form 3356 that is available through the FDA website. Establishment information is entered on the left side of the form, and the listing information is entered on the right. It can be submitted to the FDA by mail or fax, or electronically through the internet. Electronic submissions are encouraged. Currently, over 70 percent of submissions are electronic. The website has instructions for registering electronically, as well as contact information for registration-related questions.

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This slide shows a snapshot of the current distribution of registered establishments in the database. You will notice there are a significant number of firms whose registration status is inactive. The reason for this is that a number of firms registered with FDA were not required to do so. When it becomes evident that registration of such establishments is not required, the registration status reverts to inactive. Also, FDA requires distributors of human cell and tissue products to register. There are a lot of independent distributors in existence that primarily distribute medical devices. Such distributors register because they are planning to start distributing HCT/Ps. However, when their plans never materialize, or they stop distributing HCT/Ps, their registration is made inactivate.

The majority of active establishments are manufacturers of musculoskeletal and ocular products. Hematopoietic stem cell establishments rank next in the number of registered establishments, followed by establishments that handle reproductive tissues like semen banks and in vitro fertilization clinics that screen and test donors for anonymous and directed donation.

Also of note is that nearly 300 international firms are registered with FDA. The majority of these registrants import or plan to import hematopoietic progenitor cells listed in international registries. As previously mentioned, these firms that import HCT/Ps to the U.S. are required to register with the FDA.

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As a reminder, the focus of Part 1271 is to prevent the introduction, transmission, and spread of communicable disease. This starts with assessing the source of the cells and tissues. Subpart C sets out the requirements to do so through the donor eligibility determination. The determination is based on the results of donor screening and donor testing for certain communicable diseases. An HCT/P must not be implanted, transplanted, infused, or transferred until the donor has been determined to be eligible. That is, this process has to be completed and reviewed before the donor tissue can be utilized.

There are some exceptions to when a donor eligibility determination is not required, for example, when the HCT/P is for autologous use or is reproductive cells or tissue from a sexually intimate partner.

Furthermore, there are limited situations when cells and tissues from a donor found to be ineligible can be used. For example, in cases of documented urgent medical need for hematopoietic stem cell donations when there is no comparable HCT/P available and the recipient is likely to suffer death or serious morbidity without the donated cells. There is also an exception to allow for family-related donors for allogeneic use in first- and second-degree blood relatives, even if the family donor might have a risk factor or test result that would make them otherwise ineligible. A similar allowance is made for directed donation for reproductive use where a gamete donor knows and is known by a specific recipient before donation. With certain labeling and notification criteria, in these situations the use of HCT/Ps from donors who are determined to be ineligible is allowed.

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According to the regulations, HCT/P donors must be screened for risk factors for and clinical evidence of disease. Donor screening includes the medical history interview for relevant risk factors or conditions, a physical assessment of a nonliving donor, or examination of a living donor looking for physical evidence of disease, and a medical record review looking for clinical evidence of disease. For screening of nonliving donors, available medical records might include coroner records or an autopsy report that could provide information to help assess the risk for communicable disease.

The testing for donors must be done using an appropriate FDA-licensed, approved, or cleared donor screening test in accordance with the manufacturer's instructions. The testing must be performed in a CLIA-certified laboratory or other laboratory that has met equivalent requirements as determined by the Centers for Medicare and Medicaid Services. There are not very many CLIA-certified labs outside of the United States.

FDA has published a guidance document on the donor-eligibility determination that addresses many donor screening and testing issues with many useful examples. The guidance documents themselves are not legally binding, but provide FDA's current thinking on certain issues. They can be found on the FDA website.

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The eligibility determination is based upon donor screening and testing for relevant communicable disease agents or diseases. Part 1271 defines these by listing some like HIV and Hepatitis by name as well by providing criteria that allows for the addition of emerging or newly identified agents like West Nile virus.

All HCT/P donors must be screened and tested for HIV1 and 2; hepatitis B and C; and syphilis. Screening for transmissible spongiform encephalopaties is required, including CJD, as there is no licensed test available. There is also a

screening requirement for West Nile Virus, recent smallpox vaccination, and sepsis.

Consistent with the risk-based approach, there are some agents that are considered relevant for only certain tissues, and FDA requires screening and testing accordingly. Donors of reproductive cells and tissues must be screened and tested for "Chlamydia trachomatis" and for "Neisseria gonorrhoea." Leukocyte-rich cells and tissues would include semen and those of hematopoietic origin. Donors of these cells and tissues must be screened and tested for HTLV and CMV, although a donor found to be positive for CMV is not considered ineligible.

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The next subpart of Part 1271, Subpart D, describes the requirements that manufacturers must follow to ensure that HCT/Ps do not contain communicable disease agents, are not contaminated, and do not become contaminated during manufacturing. These current good tissue practice requirements prevent the introduction, transmission, or spread of communicable diseases including viruses, bacteria, fungi, parasites, and Transmissible Spongiform Encephalopathy agents. They govern the methods used in, and the facilities and controls used for, the manufacture of HCT/Ps. Again, the definition of manufacture includes any or all steps in the recovery, processing, storage, labeling, packaging, or distribution of a human cell or tissue.

Because of the wide range of tissues covered, the goals are broad and they are designed to allow the manufacturers flexibility in meeting the requirements. Most of the Good Tissue Practices are not as specific as good manufacturing practices for a licensed biologic product or the quality system regulations for medical devices. The establishment must determine how to meet these goals through their own procedures.

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This slide shows the list of what is covered in current good tissue practices. As you see, it is comprehensive, covering steps at the beginning of the process, like the donor-eligibility determination and recovery, to steps at the end, like distribution and tracking. FDA has published a guidance document, to help manufacturers comply with these requirements.

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Now let's review a few of the CGTP requirements which will give you a better understanding of their overall level of detail, and a sense of how they help meet the goals of CFR Part 1271. One is a requirement that procedures need to be established and maintained to meet current good tissue practice for all steps that are performed during manufacture of the HCT/P. You can see that it is a pretty general requirement and allows the manufacturer to determine what is best in designing and implementing the procedures as long as they are designed to

prevent circumstances that increase the risk of the introduction, transmission, or spread of communicable diseases through the use of HCT/Ps. According to this regulation, such procedures need to be reviewed, approved, available to personnel, and followed.

By regulation, the manufacturer can adopt standard procedures from another organization. For example, the American Association of Tissue Banks is an industry association that has very detailed standards. The member manufacturers can adopt and utilize the procedures that are in the standards that also conform to the corresponding FDA regulations.

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The Good Tissue Practices include a requirement for the creation of a record when any action needs to be documented. There are some specific requirements for what the record must include, such as the identity of the person performing the work, and a complete history of the work performed. Such manufacturing records must be retained for at least 10 years after administration of the product.

There are other records that have to accompany the HCT/P when distributed, including a distinct identification code affixed to the HCT/P container, as well as a statement whether the donor has been determined to be eligible or ineligible through screening and testing with a supporting summary of records.

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Another good tissue practice requirement addresses how establishments track their products. FDA requires a method for tracking the product from the donor to the consignee usually the hospital or physician that uses the cells or tissues - and from the consignee to the donor. Each HCT/P must be assigned and labeled with a distinct identification code that relates the HCT/P to the donor and to all records pertaining to the HCT/P. These tracking requirements will facilitate the investigation of an actual or suspected transmission of communicable disease, and the appropriate and timely corrective action.

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The last two subparts of 21 CFR Part 1271 are only applicable to HCT/Ps that are regulated solely under Section 361 of the PHS Act.

Consistent with the goals of Part 1271, FDA requires reporting of events that are or may be related to risk of communicable disease transmission. There are two types of HCT/P reporting: adverse reactions in the recipient where there is a reasonable possibility that the reaction was caused by the HCT/P, and deviations that happen during manufacture where it is determined that there is the possibility of contamination of a distributed product.

Shortly, this presentation will briefly review the labeling requirements that apply specifically to HCT/Ps regulated solely under the regulations in 21 CFR Part 1271.

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According to the HCT/P adverse reaction reporting requirement, manufacturers must investigate adverse reactions that involve a communicable disease related to an HCT/P made available for distribution. The manufacturer is further required to report the reaction within 15 calendar days, if it is fatal, causes permanent damage, or necessitates medical or surgical intervention including hospitalization. This is done through our MedWatch system. The form and instructions can be found on the FDA website.

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The second type of required HCT/P reporting is deviation reporting. Similar to adverse reactions, all deviations related to distributed HCT/Ps must be investigated, but only certain ones need to be reported as described in the regulation. These include deviations that occurred within the responsible manufacturer's facility or in a contract facility that performed a step in the manufacturing process. HCT/P deviations must be reported within 45 days of discovery. A form and instructions are available on the FDA website.

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In addition to the reporting requirements, Subpart E also includes labeling requirements that apply only to HCT/Ps regulated solely under the regulations in 21 CFR Part 1271. These include information that must be included on the label, such as description of the product, expiration date, and required warnings. Other label information, such as storage temperature, other warnings, and instructions for use must either appear on the label or accompany the product. Note that these labeling requirements are not as detailed as those required for a drug, device, or licensed biologic product.

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The last subpart, Subpart F, is also only applicable to HCT/Ps regulated solely under Section 361. It describes the inspection process that occurs with or without prior notification, with a frequency at the discretion of the agency. FDA inspectors work in district offices throughout the United States, as well as overseas, to inspect foreign establishments importing HCT/Ps into the United States. During an inspection, FDA may take samples, question personnel, and review and copy records. Procedures are followed to maintain confidentiality of donor and recipient information.

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The last part of subpart F addresses other aspects of inspections and enforcement. When a manufacturer is importing tissues to the United States, information must be supplied to the FDA district office at the port of entry. This

requirement does not apply to certain imported HCT/Ps that are life-saving or perishable, such as hematopoietic stem cells or reproductive tissues. These can generally be transported directly to the consignee without being held for an admissibility decision.

The second issue addressed is a description of actions that may be taken if our inspectors find violations of regulations, and therefore inadequate protection against the risk of communicable disease. The FDA can order a recall of the violative product or, for particularly egregious violations, even cessation of manufacturing.

SLIDE 26
This slide shows some useful resources.

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This concludes the presentation, "FDA Regulation of Human Cells and Tissues".

We would like to acknowledge those who contributed to its development. Thank you.