FDA Regulation of Human Cells and Tissues

SLIDE 1

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 development of the regulatory approaches and a description of the cells and tissues covered under Title 21 of the Code of Federal Regulations, or CFR, part 1271.

SLIDE 2

In the early 1990's, the U.S. 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 viruses, 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, or PHS 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 more cells and tissues, but at the same time was tiered and risk-based to allow FDA to exercise regulatory oversight only to the degree appropriate to protect the public health. When FDA announced this approach, it explained that this approach applied to human cells, tissues, and cellular and 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 rules. These rules are now codified under 21 CFR part 1271 and became effective on May 25, 2005.

SLIDE 3

21 CFR part 1271 provides the basis for regulation of all HCT/Ps, and for some of these products, the so-called "361 HCT/Ps", it is the sole regulatory requirement. FDA regulates these products under the authority of Section 361 of the PHS Act which addresses the prevention of the introduction, transmission, or spread of communicable diseases. To be regulated solely under this authority, an HCT/P must meet all four

criteria described in 21 CFR part 1271.10(a). Such HCT/Ps do not undergo pre-market review. A broad range of HCT/Ps 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 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 as well as the tissue regulations in part 1271.

Applying the tiered, risk-based approach in this way helps prevent improper handling or processing that might contaminate or damage tissues while ensuring that clinical safety and effectiveness are demonstrated for HCT/Ps that are highly processed, used for purposes considered non-homologous, combined with another article that raises new clinical safety concerns, or that have a systemic effect.

SLIDE 4

First, we need to understand what is considered an HCT/P. By regulatory definition, an HCT/P includes any article containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. This encompasses a wide variety of products that are all regulated by FDA.

SLIDE 5

This table provides examples of cells and tissues that are considered HCT/Ps and are regulated as 361 HCT/Ps, biologics, or devices. These examples are not meant to be inclusive, or detailed, that is to say that these are generalities and are provided for guidance only. The examples in the first column are generally regulated as 361 HCT/Ps provided they meet all the criteria described in 21 CFR part 1271.10(a), such as bone, tendon, cartilage, ocular tissue, skin, and reproductive cells and tissues.

Examples of HCT/Ps regulated as biologics include unrelated allogeneic hematopoietic stem cells, allogeneic pancreatic islets, and cultured cartilage cells.

Examples of HCT/Ps regulated as devices include a product that contains tendon tissue, cancellous bone, and a polyester suture for use in ligament reconstruction; and demineralized bone with certain handling agents, such as glycerol, sodium hyaluronate, or gelatin.

SLIDE 6

The products listed on this slide are specifically excluded from the definition of HCT/P. 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 vascular composite allografts and minimally manipulated bone marrow are overseen by the Health Resources and Services Administration.

SLIDE 7

As mentioned earlier,
the 1271 tissue regulations became effective on May 25, 2005. The regulations under this part are divided into six subparts: general provisions, establishment registration and listing, donor eligibility, current good tissue practice, additional requirements, and inspection and enforcement.

SLIDE 8

Subpart A explains the scope and purpose of the tissue regulations and provides definitions of certain terms used in the regulations. One purpose of the tissue regulations in 1271 is to create an electronic registration and listing system for establishments that manufacture HCT/Ps. The other purpose is to establish donor eligibility, current good tissue practice, and other procedures to prevent the introduction, transmission, and spread of communicable diseases by HCT/Ps. An example of an important term described in this subpart is manufacture. Manufacture is defined as any or all steps in the recovery, processing, storage, labeling, packaging, or distribution of human cells or tissues or in the screening or testing of cell or tissue donors. 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.

SLIDE 9

Subpart A also delineates the four criteria that a product must meet to be regulated solely under Section 361 of the PHS Act. 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 21 CFR part 1271, and no premarket submission would be required. Subpart A also describes certain well-defined exceptions from the regulations.

SLIDE 10

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 by the establishment. Registrations must be submitted electronically within 5 days after beginning operations. The registration must be updated at least annually even if there have been no changes, except that changes to ownership, location, and agent information must be updated within 30 days of the change. If changes are made to the HCT/Ps being manufactured, the establishment must update their listing at the time of the change or in each June or December, whichever month occurs first after the change.

SLIDE 11
Foreign establishments that offer HCT/Ps for import into the United States must register and list. They must identify a U.S. agent who is located in the U.S. and has a U.S. address and phone number. The U.S. agent must assist with communication to the foreign establishment and scheduling inspections. The expectation is that all HCT/Ps distributed in the U.S. are manufactured in accordance with FDA regulations.

SLIDE 12
FDA will assign each location a permanent registration number. It is important to emphasize that registration is not the same as a pre-market review, nor does it ensure an establishment is in compliance with all regulations. FDA determines compliance through periodic inspections. Registration provides the FDA with a list of establishments to inspect, and products they manufacture. Once an establishment registers, it can market and distribute HCT/Ps before an inspection by the FDA.

SLIDE 13
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, in other words the donor. Subpart C sets out requirements to do so through the donor eligibility, or DE, determination. The DE 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's cells or tissue can be used.

There is one exception in which an HCT/P can be used prior to completion of the DE determination. This is for cases of documented urgent medical need in which there is no comparable HCT/P available and the recipient is likely to suffer death or serious morbidity without the HCT/P. In the event of documented urgent medical need, HCT/Ps may also be used from a donor found to be ineligible. Additional limited uses of HCT/Ps from an ineligible donor also exist, such as HCT/Ps for use in a 1st or 2nd degree blood relative of the donor.

There are some exceptions in which a donor eligibility determination is not required, for example, when the HCT/P is for autologous use or is for reproductive use in a sexually intimate partner of the donor. Additional exceptions have also been provided for embryos for reproductive use. To use an HCT/P under any of these situations, special labeling requirements described in the regulations must be followed.

SLIDE 14
According to the regulations, HCT/P donors must be screened for
- risk factors for infection,
- and clinical evidence of
infection,
with relevant communicable diseases. Donor screening includes review of a current 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 review of medical and other records to look for risk factors for, or clinical evidence of, disease. For screening of nonliving donors, available medical records might include coroner or autopsy reports or other available records that could provide information to help assess the risk for communicable disease.

A donor specimen must be tested for evidence of infection. This testing must be done using an appropriate FDA-licensed, cleared, or approved donor screening test in accordance with the test kit manufacturer's instructions for use. The testing must be performed in a laboratory certified under the Clinical Laboratory Improvement Amendments, or CLIA, or other laboratory that has met equivalent requirements as determined by the Centers for Medicare and Medicaid Services. There are few CLIA-certified laboratories outside of the United States.

Subpart C also contains requirements related to 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.

FDA has published several guidance documents on the donor eligibility determination that address many donor screening and testing issues with many useful examples. The guidance documents themselves are not regulations, but instead provide FDA's current thinking on certain issues related to regulations. They can be found on FDA's tissue guidance website.

SLIDE 15

The eligibility determination is
based on screening and testing of the donor for relevant communicable
disease agents or diseases. Part 1271 defines these by listing some like HIV and syphilis by name as well by providing criteria that allows for the addition of emerging or newly identified agents, such as Zika virus, and these new additions are communicated through guidance.

Currently, all HCT/P donors must be screened for HIV types 1 and 2; hepatitis B and C viruses; Treponema pallidum, the agent that causes syphilis; transmissible spongiform encephalopathies, or TSEs, including CJD; West Nile virus; Zika virus; sepsis; and vaccine from a recent smallpox vaccination. Of these, all donors should also be tested for HIV, hepatitis B and C viruses, syphilis, and for living donors, West Nile virus.

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 Neisseria gonorrhea. Donors of leukocyte-rich cells and tissues such as semen and hematopoietic progenitor cells must be screened and tested for HTLV

and CMV, although a donor found to be positive for CMV is not necessarily considered ineligible since CMV has not been identified as a relevant communicable disease agent.

Details regarding the specific screening approaches and types of tests that FDA considers appropriate to meet these requirements are described through guidance documents available on FDA's website.

SLIDE 16

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 TSE 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 of this subpart are broad and are designed to allow manufacturers flexibility in meeting the requirements. Most of the current good tissue practice requirements are not as specific as good manufacturing practice for a licensed biological product or the quality system regulations for medical devices. The establishment must determine how to meet these goals through their own procedures.

SLIDE 17

This slide shows the list of what is covered in current good tissue practice requirements. 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.

SLIDE 18

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. This is a rather 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, and followed, and they must be readily available to personnel.

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 in the standards that also conform to the corresponding FDA regulations.

SLIDE 19

Current good tissue practice includes a requirement for the creation of a record concurrently with each manufacturing step. 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, or if the date of administration is not known, then at least 10 years after the date of the HCT/Ps distribution, disposition, or expiration, whichever is latest.

SLIDE 20

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 and from the consignee to the donor. The consignee is usually the hospital or physician that uses the cells or tissues. 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 a communicable disease and the appropriate and timely corrective action.

SLIDE 21

Subpart E is applicable to non-reproductive HCT/Ps described in 1271.10 that are regulated solely under Section 361 of the PHS Act.

Consistent with the goals of part 1271, subpart E 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 there is the possibility of contamination of a distributed product.

This subpart also describes labeling requirements that apply specifically to non-reproductive HCT/Ps regulated solely under the regulations in 21 CFR part 1271.

SLIDE 22

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 FDA's website.

SLIDE 23
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 deviations related to core CGTPs 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 FDA's website.

SLIDE 24
In addition to the reporting requirements, Subpart E also includes labeling requirements that apply only to nonreproductive HCT/Ps regulated solely under the regulations in 21 CFR part 1271. These include information that must be included on the label, such as a description of the product, expiration date (if any), 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 HCT/P. Note that these labeling requirements are not as detailed as those required for a drug, device, or licensed biologic product.

SLIDE 25
The last subpart, Subpart F, applies only to HCT/Ps regulated solely under Section 361 of the PHS Act. This subpart describes the inspection process which occurs with or without prior notification and at a frequency of the FDA's discretion. 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.

SLIDE 26
The remainder of subpart F addresses other aspects of inspections and enforcement. When a manufacturer offers HCT/Ps for import into 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 such as peripheral blood stem cells regulated solely under section 361 of the PHS Act or reproductive tissues donated by a sexually intimate partner of the recipient. These can generally be transported directly to the consignee without being held for an admissibility decision at the port of entry.

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

SLIDE 27
This slide provides URLs for some useful resources related to FDA's regulation of HCT/Ps.

SLIDE 28

If you have questions related to FDA's regulation of HCT/Ps, we encourage you to contact FDA. This slide provides information for contacting FDA's Center for Biologics Evaluation and Research by phone or email.

SLIDE 29

This concludes the presentation, "FDA Regulation of Human Cells and Tissues.". We would like to acknowledge those who contributed to its development. Thank you.