Cellular Therapy Products

SLIDE 1
This presentation will discuss the regulation of cellular therapies.

SLIDE 2
Manufacturing of cellular therapies is reviewed in the Division of Cell and Gene Therapies in the Office of Cellular, Tissue and Gene Therapies. This slide shows the organizational chart for the Division of Cell and Gene Therapies. The division consists of two product review branches: gene therapy and cell therapy.

The division also has three branches that conduct laboratory research, as well as product review. They are the gene transfer and immunogenicity branch, tumor vaccines and biotechnology branch, and the cellular and tissue therapy branch.

SLIDE 3
Somatic cell therapies are regulated as biologics under the Public Health Service Act section 351, in contrast to human tissues, which are regulated under section 361, where the primary safety concern is infectious disease transmission.

Human cells are regulated as biologics if any of the following criteria are met: they are more than minimally manipulated, they are combined with another article other than a preservation or storage agent, they are used in a way that is not homologous to their normal function, or they have a systemic effect and are dependent upon the metabolic activity of living cells for their primary function.

These criteria are sometimes referred to as kick-up factors, meaning that FDA regulated clinical development under Investigational New Drug, or IND, and premarket approval will be required for human cells that meet any one of these criteria.

SLIDE 4
The kick-up factors on the previous slide coincide with the FDA definition of somatic cell therapy that was first published by the agency in 1993. There, somatic cell therapy is defined as any autologous, allogeneic, or xenogeneic cells that have been propagated, expanded, selected, pharmacologically treated, or otherwise altered in biological characteristics ex vivo, to be administered to humans and applicable to the prevention, treatment, cure, diagnosis, or mitigation of disease or injuries.

SLIDE 5
Some examples of cell therapy products include stem cells and stem cell derived products, such as those from hematopoietic, mesenchymal, embryonic, and

umbilical cord blood, cancer vaccines and immunotherapies, such as dendritic cell vaccines, activated T or B lymphocytes, monocytes, and modified or unmodified cancer cells, allogeneic pancreatic islet cells, chondrocytes for cartilage repair, keratinocytes, fibroblasts, and hepatocytes.

SLIDE 6
Xenotransplantation products are also regulated in the cell therapy branch. This slide shows the FDA definition of xenotransplantation. Please note that the definition includes more than just cells. It also includes whole organ xenotransplantation, as well as products that have had ex vivo contact with live non human animal cells, tissues, or organs.

So, if you have embryonic stem cells that have been grown on a murine feeder layer, the product would be considered xenotransplantation by definition.

The most recent interest in utilizing xenotransplantation products has been the use of porcine pancreatic islets for the treatment of diabetes, and porcine hepatocytes for the treatment of acute liver failure. There has been intensive animal research recently and a few published clinical trials that took place overseas.

So, it is anticipated there may be an increase in activity in this field in the near future.

SLIDE 7
Here are guidelines and guidance documents put out by the U.S. government to manage the public health risks associated with xenotransplantation.

SLIDE 8
The previous slides covered what cell therapies are.
Now, let's transition to how cell therapies are regulated.

What rules apply to cell therapy regulation? The list of regulations shown on this slide from title 21 of the Code of Federal Regulations, called the CFR, all apply to cell therapy products. The tissue rules in part 1271, the biologics requirements outlined in the part 600 and 610, the investigational new drug requirements in part 312, and the drug manufacturing requirements in parts 211 and 212. Therefore, FDA uses existing regulations for drugs and biologics to regulate cell therapies. This has advantages and challenges, since the products themselves have very unique characteristics that are different from drugs.

SLIDE 9
There are some concerns that are unique to cellular products.

First, there is the size of the manufacturing lot. A lot may be a single dose, or multiple doses to treat only one patient. The challenge is that you have a limited

amount of material for lot release testing. Patient-specific lots also mean that you also have the challenge of ensuring that the correct patient receives the correct lot of cells.

The second concern is the timing of the manufacture, testing, and administration. Many cellular products cannot be cryopreserved, and must be administered as soon as possible after harvest. In these cases, testing, shipping, and administration procedures must be rapid, to ensure the quality and integrity of the cell therapy product.

SLIDE 10
Additional challenges include the reproducibility and consistency of the product lots. Because the starting material for manufacture is coming from a different patient or donor, there is inherent variability in the starting material. Every patient or donor will have a slightly different profile coming out of their biopsy, apheresis, or other cellular starting material. There can also be a lot of variability in the bioassays that are used to characterize these cells.

Another challenge is sterility; cell therapy products cannot be terminally sterilized. Aseptic processing is needed to maintain sterility.

The use of closed manufacturing systems is encouraged whenever possible.

SLIDE 11
In terms of quality control, there are a number of stages in the manufacturing process where you can exercise process control in order to ensure product quality. This includes the incoming cells or tissues, as well as ancillary materials. A qualification program should be in place to ensure that the reagents used in manufacturing are of the appropriate grade and quality for product consistency. In-process testing should be performed to monitor control of the manufacturing process.

Appropriate final product testing and stability testing are essential to ensure consistency and shelf-life of the cells.

SLIDE 12
FDA requires that the donor cells for an allogeneic product meet donor eligibility requirements, just the same as for human tissue donors.

SLIDE 13
Although cell banks for cell therapy products are different from cell banks used to produce biologics, the same testing is required. The cell bank may be from cells that have been grown in cell culture a few passages prior to final formulation. And, in cases where there are limited cell banks because you are using a primary cell that will be used to treat a couple of patients, some flexibility is allowed in

finding a balance between full master cell bank testing that would be required of any therapeutic and the minimum donor eligibility testing.

SLIDE 14
Test methods for in-process testing are not specified in regulation, but the methods outlined in 21 CFR 610 are recommended. Final product testing is required, and the specified results are dictated by regulation. Due to the nature of cell therapy products, however, FDA allows the sponsor to propose tests that are appropriate for their product.

The sponsor will be required to establish equivalence of these test methods to those described in 21 CFR 610 for licensure.

SLIDE 15
This slide shows a list of the tests required for biologics. This talk will focus on the tests for potency, sterility, purity, and identity. Cell therapy products are exempt from general safety testing. Mycoplasma may be required if the cells are cultured for an extended period of time. Cells that are not cultured or are cultured for a short period of time may be exempt from mycoplasma testing.

SLIDE 16
Sterility is a test that requires a 14 day culture period. However, most cell therapy products, unless they are frozen, can not be stored for 14 days in order to obtain the results of the 14-day sterility test. There can be flexibility by allowing a cell therapy product to be released based on in-process sterility testing results. For example, you might sample the cells while in culture 3 days prior to final harvest and administration to the patient. Before releasing the product, you would look at sterility results for the pre-harvest testing to make sure it is negative, before administering the cells to the patient.

Another option is a rapid assay, such as a gram stain. This is not a very sensitive assay, but it is quick, and can detect gross contamination. The gram stain is typically used in cases where the results of the 14-day sterility test can not be available prior to patient administration.

For these cases, the sponsor is required to have an action plan for positive sterility test results that are obtained after patient administration. The action plan should include notification of the physician of a positive result, a plan for how the patient will be treated and evaluated, and an investigation plan to evaluate the manufacturing process to prevent future positive sterility test results.

FDA encourages sponsors to use the rapid sterility test, as described in the guidance document referenced here.

SLIDE 17

Purity refers to impurities in the final product that come from the manufacturing process. Endotoxin testing is required for all biologics.

Other impurities may include residual solvents, antibiotics, or animal products that may have been used as tissue culture media additives that are not intended to be part of the final product, and could result in a hypersensitivity reaction or some other adverse event. For these types of impurities, FDA either looks for validation of the removal of the product or final product testing to ensure that the levels of these residuals are acceptable.

In some cases the sponsor will need to develop and validate the detection methods used to detect residuals.

When talking about impurities, the cellular composition of the final product, including contaminating cell types, is also of interest. If the product is a T cell therapy, for example, FDA will ask the sponsor to test for lymphocyte subsets in the final product. Unintended cell types might affect the safety of the product or the clinical outcome.

SLIDE 18
Identity testing is required, and the regulations state that identity testing is conducted to distinguish one product from another that is produced in the same facility. This is a challenge for cell therapy products because identity testing may not be able to distinguish patient-specific lots from one another. For these products, tracking, labeling, and segregation systems need to be in place in order to avoid mix ups between patient-specific products.

SLIDE 19
Potency is interpreted to mean the specific ability or capacity of the product to affect a given result. The test for potency shall consist of either an in vitro or in vivo test, or both, which have been specifically designed for each product to indicate its potency. Measuring potency for cell therapies is very challenging, so FDA has been very flexible in the approach to what is potency. Determining the biological activity and function of the cells in vitro may not translate into the cell's activity in vivo.

SLIDE 20
Potency can be measured by a direct ASS-ay for biological activity. For example, you may use a mixed lymphocyte reaction to see if T cells are active against a target cell, or measure sigh-toe-kine secretion to assess biological activity. FDA has also allowed the use of indirect measures where you could correlate cell phenotype with a function.

For example, dendritic cells might up regulate the expression of a co-stimulatory molecule, such as CD86, during activation, and high expression of CD86 could be an indirect measure of dendritic cell activation and potency.

FDA has also allowed what is called a matrix approach to potency testing, in which a number of different characteristics are looked at, and cummulatively those different characteristics define the potency of the cells. As an example, FDA typically asks for viability testing for lot release, and viability can inform you about potency. However, FDA generally does not accept viability as the only measurement of potency.

SLIDE 21
Ideally, potency testing results will be obtained for product release before you administer the product to the patient. A potency assay should be fully validated; it should demonstrate product activity and have a quantitative readout. It should be stability indicating and provide a measure of product consistency.

Referenced at the bottom of the slide is the transcript from the 2006 Advisory committee meeting on stability testing.

SLIDE 22
Often, a sponsor may tell FDA that they cannot test their final product, because the cells will die before the results are available. FDA tries to be flexible and consider all options for testing the final product.

But, in general, there is required-release testing to be performed on the final product, and sometimes that means that those results are not available before release, as described in the sterility assay.

Sometimes FDA requires the holding of the cell product to complete testing, which may affect the cells.

For example, it is required that the cell product not be administered until the gram stain results are available. FDA usually requires the product also be held for endotoxin testing results. This test can take up to two hours. However, there has been flexibility in terms of how and when the testing is done. In process testing at critical time points during manufacture provides valuable information, and helps in determining how to apply the lot release testing.

SLIDE 23
So, the last thing to cover in this talk is the additional product characterization. There is an infinite amount of characterization that you can do on any cell product. FDA wants to try and gain as complete an understanding as is possible of the cell therapy product.

So, sponsors are encouraged to look beyond just the simple lot release testing, and include additional testing, such as a full panel of markers for phenotypical analysis. They are also encouraged to look at gene and protein expression using

powerful assays, such as arrays, which gives you a large amount of data. FDA also encourages sponsors to look at other parameters of purity and activity.

To make sure a sponsor really understands their product, it is suggested that sponsors make use of these additional assays to conduct stability and comparability testing, to make sure that they really understand that their product is stable, and that their product is the same from before and after process changes.

Oftentimes the minimum lot release testing is not really sufficient enough to tell you everything you need to know about the product.

SLIDE 24
This slide shows two guidance documents that are relevant to the review of cell therapy products.

SLIDE 25
This concludes the presentation, "Cellular Therapy Products".

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