Combination Product Review Issues

SLIDE 1

Combination products are defined in FDA regulations found at Title 21 of the Code of Federal Regulations, Part 3.2, as products made from combining two or three of the principal FDA-regulated medical products, namely biologic, drug, or medical device. Combination products can be created in several ways; namely, they can be physically, chemically or otherwise combined; they can be packaged together; or they can be packaged separately, but labeled to be used together. This presentation will discuss several cellular therapy-device combination product scenarios, to illustrate the combination product review as it most often occurs in the context of products reviewed by the Office of Cellular, Tissue and Gene Therapies.

SLIDE 2

This is a graphical representation of the regulatory schemes that apply to cellular therapy-device combination products. The principles behind the application of the regulatory schemes in combination products is that each part of a combination product, known as a constituent part, is most appropriately regulated by the same regulations as if it were used independently. However, there is recognition that when used in a combination product there may be some overlapping regulations. In the case of overlapping regulations there is the ability to choose the most scientifically appropriate regulations for the combination product.

In the biologic-device combination products discussed in this presentation, the biologic component is a cellular therapy product. Cellular therapy products are a subset of the broader category of biologics derived from human tissue known as a human cell, tissue, or tissue- derived product, abbreviated as HCT/P. A set of regulations known as the "tissue rules," found in 21 CFR section 1271, apply to the HCT/P products when they are used as independent products and as constituent parts of a combination product. The tissue rules focus on prevention of infectious disease by HCT/P, and are designed to work together with the more general biologic regulations, including those that ensure the safety, purity, and potency of licensed biologic products.

The device regulations are similarly applied to the device-constituent part of the combination product.

Both the biologic and device regulations are used when scientifically appropriate to regulate the combination product.

SLIDE 3

The first of the two combination product scenarios discussed is the combination of a biologic product, namely, a cellular therapy that is investigated and will be labeled for use with a specific delivery catheter. This talk will only provide an overview of the situation, however the agency recently issued final guidance on the subject entitled "Cellular Therapy for Cardiac Disease," available by following links to the cellular and gene therapy pages of the agency website, at www.fda.gov. This slide references the web page for the guidance.

SLIDE 4

This slide is an example of such a catheter, designed to deliver cellular therapies directly to the myocardium in the wall of the left ventricle. The citation shown on this slide is the source of the figures, and is also a site for one of numerous articles that report the clinical trials in which this catheter has been studied. This site is an entry point into the published literature on this subject.

SLIDE 5

The biologic and the device are studied together, and the marketing authorizations would be for both the biologic and the device. Because the cells contribute the primary mode of action for the combination product, the Center for Biologics, Office of Cellular, Tissue and Gene Therapies provides the administrative and review leads for reviewing this type of combination product. The Center for Devices and Radiological Health, Office of Device Evaluation, Division of Cardiac Devices provides consult reviews on the delivery catheter. This consult will include input on engineering, preclinical, and clinical facets of the trial.

SLIDE 6

This is a slide that graphically shows the "review silos" that represent a generalized breakdown of review responsibilities, which result naturally from the scientific questions posed by the constituent parts of a cellular therapy-device combination product. These scientific differences are reflected in the scientific expertise of the reviewers and the administrative structure of the respective Centers. A selection of the most important review steps are shown within the boxes on the chart. Please note the general parallelism of the review processes conveyed in the chart. However, to accomplish the review of such combination products, reviews from both centers are involved in an ongoing dialogue with each other and with the sponsor, though that is not reflected on this graph.

Although the principal review of the manufacturing of the cellular product is conducted by the Center for Biologics, and the principal review of the catheter is conducted by the Center for Devices shown here in the yellow boxes and orange boxes, respectively, there is always an eye toward the need to evaluate the individual constituent parts, with an eye toward their eventual use together in preclinical animal studies and clinical trials, as shown graphically in the blue

boxes. At these later stages of review, the review is highly interactive among the two centers, as integration of their independent reviews is essential to arriving at a review that is adequate to assess the safety of the combination product for clinical trials, and eventually for determining that its safety and effectiveness are sufficient to allow marketing of the combination product.

SLIDE 7

This slide elaborates on the yellow boxes from the previous slide, and shows what the biologics reviewer would look at in terms of the cellular portion of the combination product. Two issues that would be evaluated are product safety and product characterization. Product safety testing would include donor screening, testing of the final product for adventitious agents, tumorigenicity, and pyrogenicity. Animal studies on the cellular component of the combination product may also be conducted as part of the product safety testing. These studies may not include the device portion of the combination product.

Product characterization includes identity testing, testing for viability, and testing for potency. These issues are discussed in more detail in the cell therapy presentation.

SLIDE 8

This slide elaborates on the orange boxes in the previous slide outlining the review silos, and describes what the device reviewer would look at in terms of the catheter portion of the combination product. Evaluations of the injection catheter can be done by animal studies, in bench testing, or a combination of both. One of the things that is critical for the use of catheters to deliver cell therapies, is the reliable delivery of specified volumes and numbers of cells, while maintaining cell viability and function after passage through the catheter. In addition, it is important to evaluate the success rate of the injections, particularly for the intra-myocardial injected products.

SLIDE 9

This slide expands on the highly integrative review steps that are shown in the blue boxes on the silo slide. There are several questions that need to be considered: to determine the effect of the catheter on the cells, what happens to cell viability? Do the cells stick to the catheter? Is the cell suspension too concentrated? Do the cells function as expected after being passed through the catheter?

Pre-clinical evaluations are needed to assess safety and proof of concept. Evaluation of clinical safety and effectiveness are done together at both centers, because adverse events observed during clinical trial can be related to the device or biologic, or a combination of the device and biologic. There may also be cases where the cause of an adverse event is not clear.

SLIDE 10

Just to highlight the importance of the integration of the review with this type of combination product, this published study shown in the slide illustrates a situation that would require an integrative approach to review, and would have a significant effect on the clinical investigation of a potentially therapeutically active biologic product. This study shows the importance of integrative and specific biocompatibility studies. This study was conducted using an ad-no-virus for human gene therapy, and showed that the catheter changed the activity of the gene expression. The study concluded that the adenovirus was sticking to the catheter, and when it was injected, the actual dose delivered was significantly less than the intended dose.

SLIDE 11

Another variation on this theme frequently seen is that of the cell-scaffold combination product. This is also an example of a biologic-device combination product, but in this case the biologic component, a cellular therapy product, is physically combined with the scaffold, and both are delivered to the patient together and act as a unit on or in the patient.

SLIDE 12

The definition of a cell-scaffold product varies, depending on country and the regulatory authority.

In the United States, cells seeded on scaffolds are considered to be combination products; the cells, of course, are the biologic, and the scaffold is a device. In the European Union, cells with a scaffold are regulated under the advanced therapy medicinal product directives as viable cells with a scaffold. These products may be referred to as tissue engineering, or regenerative medicine products, cell therapy combination products, or ATMPs -- advanced therapy medicinal products.

But, regardless of what you call them, the scientific and medical questions are the same: are these products safe and efficacious and what are the risks and benefits of widespread use?

SLIDE 13

There are three main groups of questions that come up repeatedly in the review of cell-scaffold products: One, what do you need to know about the product or its components to assess the risk or benefit of the product?

Two, at what stage of product assembly will the most accurate product information be obtained? For example, if you have a cellular or gene therapy component that will be applied to a scaffold, it might be easier to test the cells while in solution, such as in cell culture medium, rather than testing the cells once they are applied to the scaffold. An example of this type of testing would be cell viability.

Related to the first two questions is the third question: what testing methods are currently available, and what test methods need to be developed or standardized? The list of methods available to test cell-scaffold products is relatively short, while the list of which tests need to be developed and/or standardized is quite large. The Office of Cellular, Tissue, and Gene Therapies is actively involved in facilitating the development of new test methods and standardization of test methods across this product area, with the available resources and in its role as a regulatory authority.

SLIDE 14

This slide is similar to the one shown for the biologic with a delivery device. The real difference in this slide is that the cell and device or scaffold could be combined and tested before pre-clinical testing, and at any time during the manufacturing process, depending on the product-specific characteristics of the manufacturing process. Cells with a delivery device are defined as a combination product, because the two are labeled to be used together; while a cell-scaffold combination product is such because the cells and scaffold are physically combined. In this case, the cell and scaffold may be combined in culture as part of the manufacturing process. This leads to the question: what does one measure for final product release? How is one going to measure safety, identity, purity, potency of cell therapy product? And, how does one measure device performance to know that your final product is consistent and reflects what was done in the investigational trial?

This presentation provides several examples about how biologic-device combination products are regulated at FDA.

Slide 15

This concludes the presentation, "Combination Product Review Issues".
We would like to acknowledge those who contributed to its development. Thank you!