FDA
Center for Biologics Evaluation and Research
Cellular, Tissue and Gene Therapies Advisory Committee

Meeting #38
March 3, 2005

Cellular Therapies for Repair and Regeneration of Joint Surfaces

Questions for Committee Discussion

1. Confirmatory clinical studies are controlled studies designed to test hypotheses generated from the exploratory clinical studies. They should provide definitive information for licensure or marketing approval. The primary endpoint for a confirmatory clinical study should be a clear, meaningful measure of clinical benefit. Please discuss the extent to which each of the endpoints listed below meet this need. Please cite any other endpoints you regard as important for confirmatory clinical studies. Please note that the list includes some endpoints that have been regarded as clearly clinically meaningful measures and others that have been regarded as useful but not definitive measures of clinical benefit.

    a. Changes in knee function as measured by scoring systems such as the WOMAC function score.

    b. Changes in pain as measured by scoring systems that take medication usage into account.

    c. Changes in clinical examination findings (e.g., range of motion, patient's global assessment, etc.).

    d. Changes in the appearance of the joint surface on arthroscopy and histopathological appearance of a biopsy sample from the treated site. Please also discuss whether the potential morbidity entailed by biopsy outweighs its utility as an endpoint.

e. Changes in the appearance of the joint surface and joint space on Magnetic Resonance Imaging or other noninvasive techniques (e.g., X-ray, computerized tomography, etc.).

2. Confirmatory clinical studies should provide robust, verifiable evidence of the clinical benefit afforded by a cartilage repair product. Please discuss the importance and limitations of the following aspects of clinical study design for sponsors to consider when designing confirmatory clinical studies. Please highlight those situations where flexibility may be acceptable and identify any ancillary considerations that might optimize the clinical study design.

    a. The nature of the control group; for example, active product or active dose comparator, surgical procedure comparator, historical comparator, etc.

    b. The importance of blinding procedures; for example, complete blinding versus the use of blinded evaluators or other options.

    c. The duration of the clinical studies, as it relates to assessing short term as well as long term benefit in time weighted or landmark analyses. Specifically, at what time points should important endpoints be evaluated in order to assess the success and durability of a treatment effect?

3. Please discuss the limitations and capabilities of available animal models for predicting safety and clinical activity, focusing on the following:
    a. How should questions of dose and allometric scaling (i.e., size and shape of animal joint versus size and shape of human joint) be explored in animal models?
    b. To what extent do differences between human versus animal anatomy and cell physiology need to be addressed in an animal model that uses analogous animal cells to model human chondrocyte function? Which specific interspecies differences affect the types of conclusions that can be drawn from animal studies?
    c. Are non-invasive imaging modalities such as ultrasound, CT, or MRI adequate as a replacement for interim sacrifices in long-term (six to eighteen month) studies to evaluate for intraarticular toxicity and /or cartilage formation?

d. What role should biomechanical tests play in analysis of cartilage repair in animal models?
e. What role should arthroscopic biopsy play in analysis of cartilage repair in animal models?
f. Are tumorigenicity studies needed for cultured chondrocyte cellular products?

4. Please provide specific comments on the following with respect to a "pivotal" animal toxicology study that is designed to support a clinical trial of a cellular cartilage repair product?
    a. What animal model(s) and study duration are needed to support exploratory clinical trials?
    b. What animal model(s) and study duration are needed to support a licensing application?
    c. Traditionally, *in vivo* toxicology studies include measures of systemic toxicity such as clinical pathology tests and histopathology of major organs. Is this approach warranted for toxicology studies with the following categories of products:
        i. cellular products?
        ii. modified cellular products that may secrete molecules capable of producing systemic toxicities (e.g., *ex vivo* gene therapy)?

5. For an allogeneic cellular product for articular repair, what, if any, additional safety concerns beyond those posed by an autologous product should be addressed in an *in vivo* study prior to initiation of clinical trials?

6. Characteristics of the starting tissue, which could be derived from the involved joint or a different site, may influence the quality of the cellular product substantially. Please discuss what criteria should be used for obtaining such tissue (e.g., anatomic site, pathologic involvement of the tissue to be collected, etc.). Please discuss the gross characteristics that would be useful, including those that may be visible at operation before excising the biopsy, and/or microscopic or molecular characteristics evaluated following collection but before use.
7. Noting that cells intended for repair of joint surfaces, when grown in vitro, may not express characteristics of cells that produce differentiated cartilage, please consider the

following question: What characteristics (e.g., based on analysis of proteins, extracellular matrix components, mRNA expression levels, cell surface antigens, cellular morphology, functional properties, or other parameters) could be used to identify cells that will form stable chondrocytes in vivo? Where appropriate, discuss characteristics that should be absent from these products as well as those that should be present.

8. For licensed biological products, each lot of final product must be tested for identity, purity, and potency prior to clinical use. Please discuss what analytical tests and acceptance criteria could be applied to each of these parameters to provide reasonable assurance of adequate product performance in vivo.
    a. Please identify the characteristics discussed under question 7 that would be useful in developing such tests.
    b. Given the capabilities and limitations of animal models discussed previously (Question 3), please discuss how these models may be used to provide data to support the *in vitro* characterization tests.
    c. Please discuss biological activity assays that may be used to measure the potency of each product lot to ensure product consistency. Are methods based on determination of viable cells by dye exclusion (e.g., for cells used immediately after culture) or formation of colonies in soft agar (where time permits, e.g., if final product is cryopreserved) adequate? If not, please suggest appropriate alternatives.
9. Many products in this category consist of cells within a biological or artificial matrix. What special considerations (e.g., mechanical testing, histological analysis, spatial distribution of gene expression, etc.) does this present for product characterization and specifications? Please discuss in terms of product safety, purity, identity, and potency.