Guidance for Industry

Preparation of IDEs and INDs for Products Intended to Repair or Replace Knee Cartilage

DRAFT GUIDANCE

This guidance document is for comment purposes only.

Submit comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.fda.gov/dockets/ecomments. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions on the content of this guidance, contact Dr. Richard McFarland, Office of Cellular, Tissue and Gene Therapies, Center for Biologics Evaluation and Research, at 301-827-5102 or Mr. Aric Kaiser, Office of Device Evaluation, Center for Devices and Radiological Health, at 240-276-3676.

U.S. Department of Health and Human Services
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Center for Biologics Evaluation and Research
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Contains Nonbinding Recommendations

Draft – Not for Implementation

Guidance for Industry

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance document provides to you, sponsors, recommendations about certain information that should be included in an investigational device exemption (IDE) or investigational new drug application (IND) for a product intended to repair or replace knee cartilage. For the purposes of this document, a product intended to repair or replace knee cartilage, as with other articular cartilage repair or replacement products,[1] may include a biologic, device, or combination product[2] whose components would be individually regulated by the Center for Devices and Radiological Health (CDRH) and the Center for Biologics Evaluation and Research (CBER).[3,4]

This guidance supplements recommendations regarding IDE and IND submissions contained in other FDA publications (e.g., "Guidance on Applications for Products Comprised of Living Autologous Cells Manipulated ex vivo and Intended for Structural Repair or Reconstruction" (Ref. 1)). For general information on IDEs and INDs, see http://www.fda.gov/cdrh/devadvice/ide/index.shtml and http://www.fda.gov/cber/ind/ind.htm, respectively.

[1] Prostheses such as unicondylar or total knee implants are beyond the scope of this guidance. Meniscus replacement products—which are being studied for use in preventing cartilage damage—are also beyond the scope of this guidance unless manufacturers propose new indications related to cartilage repair, replacement, or preservation.

[2] A combination product is comprised of two or more different types of regulated constituents (i.e., drug-device, drug-biologic, device-biologic, or drug-device-biologic). See Title 21 Code of Federal Regulations (CFR) 3.2(e) for further information on how combination products are defined by FDA.

[3] Forward specific questions regarding the jurisdiction over a combination product to the Office of Combination Products (OCP) at 301-427-1934 or combination@fda.gov. Information about the Request for Designation (RFD) program and guidance related to the regulation of combination products are available at the OCP website (http://www.fda.gov/oc/combination). Forward questions regarding the applicability of specific regulations for articular cartilage repair or replacement products, for which jurisdiction has already been determined, to the Center with jurisdiction.

[4] Human cells, tissues, and cellular and tissue-based products (HCT/P's) regulated solely under section 361 of the Public Health Service Act (42 U.S.C. 264) and 21 CFR Part 1271 are beyond the scope of this guidance.

We, FDA, typically regard investigational devices for articular cartilage repair or replacement to be significant risk devices (see 21 CFR 812.3(m)(1)). Therefore, if you intend to conduct clinical studies of these devices in the United States, you will likely need to submit to FDA an IDE (21 CFR 812.20(a)). All investigational studies for cellular therapy products, except for HCT/Ps that meet the criteria specified in 21 CFR 1271.10(a), including products for articular cartilage repair or replacement, require submission of an IND (21 CFR 312.20). When an IND or IDE is required, you must comply with FDA's IND regulations (21 CFR Part 312) or IDE regulations (21 CFR Part 812), as appropriate, to proceed with clinical investigations of these products. Institutional review board (IRB) approval alone is generally not sufficient to commence a clinical study in human subjects involving articular cartilage repair or replacement products (21 CFR 56.103).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

We prepared this guidance to address issues that may arise in the development of articular cartilage repair or replacement products. This guidance also reflects input received from the public and the Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) at the March 3 to 4, 2005, CTGAC meeting (Ref. 2).

In addition, we carefully considered the relevant statutory criteria for FDA decision-making and any possible burden you may incur in your attempt to address the issues and follow our recommendations in the guidance. We believe that we have considered the least burdensome approach to resolving the issues presented in this guidance document. If, however, you believe that there is a less burdensome approach, we recommend that you follow the procedures outlined in the "Guidance for Industry: A Suggested Approach to Resolving Least Burdensome Issues" (Ref. 3).

III. PRODUCT DESCRIPTION

For products subject to the IDE submission requirement in 21 CFR Part 812, you should, and in some cases are required to, provide in an IDE the following information to describe the investigational device. Depending on the particular design of the product, additional information may be appropriate:

- A complete written description of the individual components and how any components interact. See 21 CFR 812.25(d) and 812.20(b)(2).
- A description of the material(s) and any voluntary material standard(s) to which the material(s) conform. See 21 CFR 812.25(d) and 812.20(b)(2). Depending on the material, we may recommend biocompatibility testing, as described in section VI.
- A description of anticipated changes to the system. See 21 CFR 812.25(d) and 812.20(b)(2).
- A list of all instruments unique to the implantation of the product, the material and voluntary material standard to which they conform, and supporting magnified sketches or photographs of them. See 21 CFR 812.25(d) and 812.20(b)(2).

For any concurrent control product or treatment, we recommend that you provide a written description, any available drawings and photographs, and information regarding materials from which the control product is manufactured.

For products regulated under an IND, we recommend that you incorporate a description of the product into the Chemistry, Manufacturing, and Controls (CMC) section of the IND submission as described in the final guidance listed below in section IV.B. and, when finalized, the two draft guidances listed in section IV.B.

IV. MANUFACTURING AND CMC INFORMATION

A. Device Component

Under 21 CFR 812.20(b)(3), you must provide a description of the methods, facilities, and controls used for the manufacture, processing, packing, storage, and, where appropriate, installation of the device, in sufficient detail so that a person generally familiar with good manufacturing practices can make a knowledgeable judgment about the quality control used in the manufacture of the device.

As part of that information, you should provide the following:

- basic manufacturing information regarding product design issues; and
- sterilization information for the finished device, as described in the guidance entitled, "Updated 510(k) Sterility Review Guidance K90-1; Final Guidance for Industry and FDA" (Ref. 4).

B. Cellular or Gene Therapy Product or Cellular Component of Combination Product

For a cellular or gene therapy product or cellular constituents of a combination product, we recommend that you refer to "Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy" (Ref. 5). When finalized, we also recommend that you refer to the following draft guidances:

- Draft "Guidance for Reviewers: Instructions and Template for Chemistry, Manufacturing, and Control (CMC) Reviewers of Human Somatic Cell Therapy Investigational New Drug Applications (INDs)" (Ref. 6); and
- Draft "Guidance for FDA Review Staff and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)" (Ref. 7).

V. NONCLINICAL DATA AND TESTING

You should provide nonclinical data sufficient to establish a scientific rationale for clinical investigation of your product, and to demonstrate an acceptable safety profile of your product prior to initiating a human clinical study (see 21 CFR 312.23(a)(8) for IND-specific requirements relating to the submission of pharmacology and toxicology information). These data can be derived from animal studies, mechanical testing, or a combination of both. You should choose the most appropriate testing to demonstrate the activities and address the safety issues raised by your product. We encourage you to design testing strategies that combine animal and mechanical testing in single studies if such a strategy does not compromise the validity of the measurements, or the usefulness of the data.

A. Animal Data and Testing

Generally, animal studies are used to assess the following issues:

- Biological response to products (e.g., biological activity [proof of concept and safety data] of each component of a combination product). You can use animal studies to demonstrate that a product's components have the potential to contribute to the clinical efficacy of the final product.
- Durability of the response (e.g., length of time needed to assess repair of the cartilage lesion and durability of the repair). You can assess durability of the response in large animal studies. Generally studies of one year in length are recommended to provide an adequate period for completion of healing and assessment of durability.
- Toxicology (e.g., potential for local and systemic toxicities due to component of the product). Local toxicities may be due to interactions of the product with the components of the joint, or degradation of the product in the joint. Systemic toxicities may be due to cell migration outside of the articular space. Potential for tumorigenicity or inappropriate differentiation of cellular products exist within or outside of the articular space.
- Dose response (e.g., effect of variation in cell number or size of lesion). Dose response can be assessed in large animal studies.

1. Suitability of animal model(s)

We recognize that choosing and determining the suitability of an animal model(s) for evaluation of any specific product is difficult because there is no perfect animal model of articular cartilage injury. As discussed at the March 2005 CTGTAC meeting (Ref. 2):

- the scientific literature contains descriptions of numerous methods for evaluating the nonclinical behavior of native cartilage and, consequently, articular cartilage repair or replacement products;
- not all of these methods may apply to a specific articular cartilage repair or replacement product; and
- goats, sheep, and horses are the most frequently used large animal models for cartilage repair.

Any of these animal species may be appropriate in studies designed to support the activity and safety of your cartilage repair or replacement product. However, we recommend that you choose the species after carefully considering the model's ability to reflect the intended clinical use.

In the case of a product containing human cells, studies performed in animals often require the use of either immunosuppressive agents to avoid rejection of the product, or the use of analogous cellular products in animals. Analogous cellular products are cellular products derived from the animal species used for testing that are analogs of the ultimate clinical product in phenotype and biologic activity. You should characterize the level of analogy with the human product in preliminary studies prior to conducting a pivotal toxicology study with the analogous cellular product.

We recommend the use of pilot studies designed to confirm the suitability of testing a particular product in a specific animal species. Several different animal studies and/or species may be necessary to adequately model functional aspects and potential toxicities of a single product. However, the number of studies needed should be determined by relevant structural and biological characteristics of the product, not by the number of components of the product. We recommend that you design nonclinical testing of cartilage repair and replacement products that contain a cellular or gene therapy component, following the principles provided in section VIII of the "Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy" (Ref. 5).

Because a recommendation for a set of specific evaluations is not possible without detailed description of the articular cartilage repair or replacement product, reference is made to the American Society for Testing and Materials (ASTM) F2451-05, "Standard Guide for *in vivo* Assessment of Implantable Devices

Intended to Repair or Regenerate Articular Cartilage," approved April 1, 2005.[5] This standard provides guidelines related to the development of animal models and mechanical testing, and we recommend that you consult this standard or the applicable scientific literature when designing animal studies. Specifically, the standard contains a:

- comparison of animal models, articular cartilage defect types, and articular cartilage defect locations;
- discussion of articular cartilage defect preparation;
- description of gross and histological assessments; and
- description of various mechanical evaluations and their applicability.

2. Animal report(s) to be submitted

You should provide complete reports of any animal studies conducted using the investigational product, whether adverse or supportive, relevant to the evaluation of the safety or effectiveness of the investigational product. For INDs, you must provide a full tabulation of data suitable for detailed review for each toxicology study that is intended primarily to support the safety of the proposed clinical investigation (21 CFR 312.23(a)(8)(ii)(b)). For each nonclinical laboratory study subject to the good laboratory practice (GLP) regulations under 21 CFR Part 58, you must include a statement that the study was conducted in compliance with the GLP regulations, or, if the study was not conducted in compliance with those regulations, a brief statement of the reason for the noncompliance (21 CFR 312.23(a)(8)(iii) for INDs and 21 CFR 812.27(b)(3) for IDEs). You should specify in the animal report the purpose of the study and provide a detailed methods section, to include the creation and location of the cartilage defect, and supporting pathological, histological, and radiological evaluations. In addition, you should describe any differences between the product used in the animal studies and the product proposed for clinical use in the IDE or IND.

B. Mechanical Data and Testing

You should provide mechanical data for all articular cartilage repair products or a rationale addressing why mechanical testing is not necessary to establish an acceptable safety profile of the investigational product.

The mechanical testing appropriate for your product may depend on the design, material, method of attachment to the subchondral bone and/or surrounding intact cartilage, and patient indication. However, you should generally provide mechanical testing results to address the ability of the implant to withstand expected in vivo static and dynamic loading (e.g., compression, shear, propensity to generate wear debris, analysis of fixation

[5] The referenced document is an American Society for Testing and Materials Standard. The standard is available at http://www.astm.org, or contact ASTM Customer Service at service@astm.org.

method). We recommend that you compare the properties of the repaired or regenerated cartilage to those of normal articular cartilage. You should determine the aggregate modulus (H_A), Poisson's ratio (ν) and permeability (κ) of the solid phase. Permeability and aggregate modulus can be determined by confined compression creep testing, while all three of these properties can be determined from creep indentation tests using porous indentors (ASTM Standard F2451-05 contains information regarding suggested test methods). You should also include an assessment of the degree of cartilage breakdown. This may be done visually after staining with India ink or indentation probe "stiffness" evaluations.

We realize that some types of products are not capable of fully withstanding applied loads at the time of implantation (e.g., a cellular product held in place by a periosteal flap or a flexible scaffold that will eventually be populated by cells that ultimately form a load-bearing tissue). For these products, it would be appropriate to characterize various properties at discrete timepoints. You should initially assess the product's ability to maintain its location within the loaded joint, and subsequently continue to assess this characteristic while adding assessments of the newly-formed tissue and its ability to bear applied loads.

When there are differences between the proposed clinical product and the product tested, you should explain how or why the results are relevant in establishing the relative safety of the proposed product. Regardless of the evaluations which are performed, you should compare the properties of the repaired or regenerated tissue to control tissue (e.g., the cartilage collected from an unoperated control joint). While it is understood that the repair tissue might have properties that differ from those of normal cartilage, you should describe why these differences might not be relevant to the in vivo and clinical behavior of the product.

You should provide complete reports of any mechanical testing conducted on the investigational product, whether adverse or supportive, that are relevant to the evaluation of the safety or effectiveness of the investigational product. Each test report should include, but need not be limited to, the following elements:

- identification of the components that comprised the product tested;
- the set-up;
- the procedures;
- rationale supporting the testing environment as being a worst case condition
- rationale for the loading modes chosen;
- the results; and
- a discussion of the results in terms of the expected in vivo and clinical performance of the system.

You should also provide a comprehensive summary of all mechanical testing in addition to complete reports for each test.

VI. BIOCOMPATIBILITY

Depending on the material(s) used in the product, we may recommend biocompatibility testing. FDA's guidance entitled, "Use of International Standard ISO-10993, 'Biological Evaluation of Medical Devices Part-1: Evaluation and Testing'" (Ref. 8) and/or ASTM F748-04, "Standard Practice for Selecting Generic Biological Test Methods for Materials and Devices"[6] may be recommended as acceptable approaches for conducting biocompatibility testing. You should include in the IND or IDE a complete test report describing the tests performed, the specific methods utilized, and the results.

In addition, for any biological or drug component (e.g., bone morphogenic protein, bovine protein), we recommend that you follow any applicable FDA guidances.

VII. CLINICAL STUDY PROTOCOLS

Clinical studies of articular cartilage repair or replacement products must be conducted in compliance with IDE regulations (21 CFR Part 812) or IND regulations (21 CFR Part 312), along with Informed Consent (21 CFR Part 50) and IRB regulations (21 CFR Part 56) and other applicable regulatory requirements.

A. Design

In general, the clinical development program for an investigational knee cartilage repair or replacement product should proceed through an orderly series of exploratory and confirmatory clinical studies. The number of clinical studies as well as the specific design requirements for each of these studies is contingent upon multiple factors, including the characteristics of the investigational product, the route of product administration, the characteristics of the target patient population and the proposed product indication. Consequently, this guidance provides only a broad outline of the major features to consider in designing a clinical study.

1. Exploratory Clinical Studies

You should design exploratory clinical studies that are conducted early in clinical development to obtain, in addition to any other features, the following information:

- safety data;
- data assessing the ability to properly administer the product, including identification of any study procedures that should be modified to optimize product administration;

[6] Id.

- bioactivity data, such as assessments of cartilage integrity based upon imaging results and biopsy findings;
- data assessing the appropriateness of the target patient population; and data providing information concerning the activity of the product in vivo or other information related to product activity that may be informative for future development such as:

    - product dose-response relationships
    - product design-response characteristics

You should comprehensively evaluate exploratory clinical study data to facilitate the design of confirmatory studies. At the conclusion of exploratory clinical studies, you should be able to provide clinical data explaining the important aspects of the proposed confirmatory clinical studies that apply to the investigational product, such as:

- data that support the product dose and design characteristics;
- route of administration, including surgical technique in the use of the product;
- extent and nature of follow-up evaluations;
- study subject sample size;
- eligibility and ineligibility criteria;
- choice of the major study endpoints; and
- statistical assessments of the major study endpoints.

An important consideration for an exploratory clinical study of knee cartilage repair or replacement products is the use of a control group(s) to optimize the interpretability of the exploratory findings. In general, the most important clinical outcomes associated with use of these products are relief of pain and restoration of knee function, outcomes we believe are highly susceptible to bias due to assessment subjectivity. The use of control groups may greatly facilitate the interpretation of the clinical study findings, even if–because of the nature of the studies–the statistical assessments lack the robustness or power expected of confirmatory clinical studies.

2. Confirmatory Clinical Studies

Confirmatory clinical studies are designed to obtain hypothesis-testing data (i.e., to test a primary efficacy hypothesis and provide sufficient supportive data for that hypothesis as well as corresponding safety data). Depending upon the characteristics of the investigational product, safety concerns may render a larger sample size appropriate than one might estimate based solely upon the size of the projected primary efficacy endpoint treatment effect. Consequently, we recommend that you consider both efficacy and safety considerations in designing confirmatory clinical studies.

Typically, confirmatory clinical studies utilize a randomized, controlled design. Whenever possible, we recommend that you utilize a randomized, controlled study design with endpoints ascertained in a blinded manner (e.g., primary endpoints should be performed in either a completely blinded manner or with the use of major endpoint evaluators who are blinded to the study treatment assignments). However, alternative confirmatory study designs may be considered; as described, for example, in existing FDA guidance for products regulated under IND.[7] You should provide us with data (from your studies and applicable literature) and a rationale to support your confirmatory study design prior to initiation of a confirmatory study for any cartilage repair product.

Listed below in section VII.B through G are important considerations for the design of both exploratory and confirmatory clinical studies.

B. Control Group

Multiple options exist for the choice of a study's control groups, and we recommend that you review the "Guidance for Industry: E10 Choice of Control Group and Related Issues in Clinical Trials" (Ref. 9). This guidance, while intended for biological products and drugs, contains concepts which, we believe, may also be relevant to the clinical study of an investigational device-biologic combination product.

In general, control groups may be broadly divided into either concurrent or historical controls. Rapid advances in surgical techniques and the medical care of damaged knees over the past several years suggest that you should generally use a concurrent control group to obtain the most informative clinical data. We believe historical controls are rarely sufficient for confirmatory clinical studies of knee cartilage repair or replacement products.

The most common types of concurrent control groups include placebo controls, sham-surgery controls, active-comparator controls, or standard care controls. If you choose an active comparator control, we recommend that you use one that is well accepted as standard treatment for the indication. For example, this comparator may be an approved or licensed product or a well-accepted surgical procedure for the indicated condition. Comparator procedures may include the following: microfracture, debridement, osteochondral autograft transplantation (e.g., mosaicplasty), autologous chondrocyte implantation, autogenous perichondral or periosteal grafts, and osteochondral allografts, depending on the standard treatment for the indication.

[7] For cell, gene therapy, and combination products regulated under section 351 of the Public Health Service Act (42 USC 264), please refer to the discussion of surrogate endpoints in FDA's "Guidance for Industry on Fast Track Drug Development Programs: Designation, Development, and Application Review" dated January 2006 (http://www.fda.gov/cber/gdlns/fsttrk.pdf).

You should provide a rationale for the selected comparator(s). This rationale should include the comparability of the experimental and control treatments with respect to the extent of the surgical procedures involved as well as the duration and extent of rehabilitation.

A study could also include more than one comparator study arm. For example, a controlled study could compare treatment effects across a range of investigational product dosages or compare treatment effects among a group of alternative procedures/products.

"Sham controlled studies" represent one study design and choice of control group which may allow for discrimination of patient outcomes caused by the test treatment from outcomes caused by other factors such as patient or observer expectations. This type of study design could be considered in studies with subjective endpoints such as reduction in patient-reported symptoms. Sham surgical procedures/treatments involve more risk than the placebo control arm in drug trials and should be used in limited circumstances. This study design should only be considered when it is methodologically necessary, i.e. when designs that are unblinded are methodologically unacceptable (e.g., because endpoints are subjective) and when a "no treatment" control is methodologically required. Furthermore, the withholding of treatment should not lead to serious harm, such as death or irreversible morbidity. FDA recognizes that it may be difficult for sponsors to develop a clinical study design with a sham control arm that investigators, institutional review boards, and patients believe is ethical; for this reason, studies involving a sham control arm should be carefully considered and planned. Additionally, if a sham procedure/treatment is being considered in a clinical investigation involving children, the requirements of 21 CFR Part 50 Subpart D (Subpart D) also apply.

We recommend that, for most studies, randomized controls be used such that the control group populations have lesions that are similar to the experimental group in terms of depth, size, and extent of cartilage/bone damage.

C. Patient Population

We recommend you prespecify the following patient selection characteristics within a study protocol's eligibility criteria:

- degree of pain;
- presence or absence of osteoarthritis and method of diagnosis of osteoarthritis;
- minimum and/or maximum degree of physical function;
- location of articular lesion (e.g., medial femoral condyle, lateral femoral condyle);
- depth of lesion;
- size area of lesion (i.e., in cm^2);
- concomitant joint pathology (e.g., meniscal tear, ligament tear); and
- whether there has been prior treatment for the lesion.

In defining each of these characteristics, you should select unambiguous definitions, preferably based upon well-accepted evaluation techniques. One acceptable way for determining subject eligibility by size and extent of the cartilage lesion is through use of the International Cartilage Rating System (ICRS), as described in the International Knee Documentation Committee (IKDC) Knee Examination Form-2000.[8] You should provide a scientific rationale in your study protocol or supportive documents for selecting minimum values, maximal values, lesion depth, and lesion size. To determine subject eligibility by clinical parameters such as pain and clinical function we recommend that you use an established clinical measurement instrument such as those described in section VII.D.

D. Study Endpoints

We recommend that clinical studies assess the endpoints described in this section. However, the applicability of these endpoints depends on the characteristics of the investigational product and its method of administration.

We believe that clinically meaningful endpoints, such as improvement in pain and physical function, provide the most persuasive evidence of efficacy. Consequently, you should identify changes in pain and/or physical functioning as the primary endpoint for confirmatory clinical studies. Examples of measures that may be used to assess these endpoints include the:

- Knee injury and Osteoarthritis Outcome Score (KOOS);
- IKDC Subjective Knee Evaluation Form-2000;
- Cincinnati Knee Rating System;
- Symptom Rating Form; and
- Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).

Depending on the primary abnormality in the target population and other study design characteristics, we recommend that you use change in knee pain and/or physical functioning as the single primary endpoint in confirmatory studies. If you use a co-primary approach, then statistical success should be met in both endpoints in a manner that preserves the overall type 1 error.

Secondary endpoints that may be studied include:

- arthroscopic assessments of changes in the size, location, and grade of cartilage lesions both before and after debridement, if debridement is intended. One acceptable method for assessing these endpoints is through use of the ICRS, as described previously in section VII.C above.

[8] This form is contained in the ICRS Cartilage Injury Evaluation Package, available at http://www.cartilage.org/_files/contentmanagement/ICRS_evaluation.pdf.

- assessment of the physical findings from examination of the knee joint, including:

    - both passive and active range of motion
    - quadriceps muscle strength
    - presence of patellar subluxation
    - presence and degree of effusion
    - alignment
    - presence and degree of crepitus
    - presence and degree of ligament laxity

- arthroscopic evaluation to assess:

    - the integrity of repaired tissue
    - the binding of implanted investigational product to adjacent tissue, including assessments of stiffness/firmness based upon tissue probing

- histologic evaluation at both short (e.g., six months) and long term (e.g., two years) follow-up in a subset of subjects to assess:

    - matrix zonal organization
    - cell density
    - cell morphology (i.e., chondrocytic vs. fibroblastic)
    - type I or type II collagen concentration
    - Aggrecan concentration, size, and composition
    - Dermatan sulfate proteoglycan concentration
    - noncollagenous protein concentrations (fibronectin, tenascin)
    - inflammatory response

- serological assessments for antibody formation and evidence of inflammation.
- assessment of synovial fluid samples for cell count, sterility and, as applicable, markers of inflammation and antibody formation.
- joint/cartilage structure as assessed by magnetic resonance imaging (MRI), for:

    - articular surface integrity
    - thickness and volume of chondral surface
    - subchondral bone plate contour
    - thickness and volume of synovial membrane
    - volume of synovial fluid

We recommend that the protocol specify which MRI techniques and views will be taken, and that the images be interpreted by at least two independent (blinded) readers. The protocol or study supportive documents should include a clear, prospectively stated, description of the plan for review of these images, and plans for resolving conflicting readings.

E. Investigational Product Administration

The clinical protocol and supportive documents must provide a detailed description of the procedures to be used in administration of the investigational product. See 21 CFR 312.23(a)(6) and 812.25(b). This description is especially critical in multi-center studies. We acknowledge that many surgical procedures use techniques common to standard surgical practice and these procedures can be briefly summarized in the description of the investigational product administration procedures. Any unique procedures for administration of the investigational product should be described in detail.

For plans related to any surgical procedures, the clinical protocol should identify and provide details on the:

- **Surgical technique** for both the investigational and control treatments, including the type of anesthesia, the size of the incision, and the use of antibiotics and pain medications, as applicable. We recommend that the surgical procedures be comparable, as much as possible, between treatment groups.
- **Plans for post-operative care**. Supportive documents should address the use of continuous passive motion; the duration, method, and frequency of weight bearing; the type, dose, and frequency of pain medication used; and the type and frequency of rehabilitation. These factors should be standardized between/among treatment groups when possible.

F. Follow-Up

You should include sufficient follow-up information for all investigational products within a premarket approval application (PMA) or BLA. For investigational products which are resorbed, degraded, or remodeled, the study subject follow-up duration should be based on information gathered from in vivo and in vitro nonclinical studies, as well as from information based upon the natural history of the underlying, target clinical condition. However, even in this situation, we recommend that the PMA or BLA include two-year follow-up safety information on a subset of study subjects (this subset of subjects could be from initial, exploratory clinical studies). Data from an extended follow-up period provides an important component of the information to be contained within product labeling. Therefore, the subjects enrolled in initial or exploratory studies should continue to be followed during the period of confirmatory studies so that you ultimately provide some long-term follow-up information from these initial studies. For reference, guidance on the length of follow-up for gene therapy products is available in

the "Guidance for Industry: Gene Therapy Clinical Trials - Observing Participants for Delayed Adverse Events" (Ref. 10).

For investigational products which are not reabsorbed or degraded, a longer duration of patient follow-up is recommended to document safety outcomes. In this situation, generally five years of patient follow-up is recommended. This may be initiated during the pre-market phase and continued post-market.

G. Adverse Event (Risk) Reporting

This section concerns adverse event (AE) reporting by the investigator(s) to you. See 21 CFR 312.64 and 812.150(a)(1).[9] When an investigator reports AEs to you, the investigator should stratify the AEs by those general to any surgery, those related to knee surgeries (open vs. arthroscopic), and those specific to the investigational product. We recommend that you incorporate definitions or descriptions of known or anticipated AEs into the case report forms (CRFs) to ensure uniform reporting. You should also state in the protocol and CRFs that all subsequent surgical interventions, investigational product-related or not, should be reported and recorded.

We define subsequent surgical interventions as follows:

- Revision - a procedure that adjusts or in any way modifies or removes part of the original investigational product, with or without replacement of a component; it may include adjusting the position of the original investigational product. If the investigational product is used/implanted in conjunction with an FDA approved product/component, a revision to any component, even to the approved component, should be reported as a revision.
- Removal - a procedure where all or part of the original investigational product is removed with or without replacement.
- Reoperation - any subsequent surgical procedure at the involved surgery site that does not involve removal, modification, or addition of any component(s) to the product.

[9] For requirements regarding adverse event reporting by the sponsors to FDA, see 21 CFR 312.32 and 812.150(b)(1).

VIII. REFERENCES

1. Guidance on Applications for Products Comprised of Living Autologous Cells Manipulated ex vivo and Intended for Structural Repair or Reconstruction, May 1996 (http://www.fda.gov/cber/gdlns/gdexv.pdf).

2. Cellular, Tissue, and Gene Therapies Advisory Committee meeting, March 3, 2005 (http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4093T1.htm); March 4, 2005 (http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4093T2_01.htm).

3. Guidance for Industry: A Suggested Approach to Resolving Least Burdensome Issues, September 2000 (http://www.fda.gov/cdrh/ode/guidance/1188.html).

4. Updated 510(k) Sterility Review Guidance K90-1; Final Guidance for Industry and FDA, August 2002 (http://www.fda.gov/cdrh/ode/guidance/361.html).

5. Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy, March 1998 (http://www.fda.gov/cber/gdlns/somgene.pdf).

6. Draft Guidance for Reviewers: Instructions and Template for Chemistry, Manufacturing, and Control (CMC) Reviewers of Human Somatic Cell Therapy Investigational New Drug Applications (INDs), August 2003 (http://www.fda.gov/cber/gdlns/cmcsomcell.pdf).*

7. Draft Guidance for FDA Review Staff and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs), November 2004 (http://www.fda.gov/cber/gdlns/gtindcmc.pdf).*

8. Guidance on Use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing," May 1995 (http://www.fda.gov/cdrh/g951.html).

9. Guidance for Industry: E10 Choice of Control Group and Related Issues in Clinical Trials, May 2001 (http://www.fda.gov/cber/gdlns/clincontr0501.htm).**

10. Guidance for Industry: Gene Therapy Clinical Trials – Observing Participants for Delayed Adverse Events, November 2006 (http://www.fda.gov/cber/gdlns/gtclin.pdf).

*These draft guidances, when finalized, will represent FDA's current thinking on their respective topics.
**International Conference on Harmonization document.