Guidance for Industry

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

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U.S. Department of Health and Human Services
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Table of Contents

Contains Nonbinding Recommendations

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I. INTRODUCTION

This guidance document provides to you, sponsors of an investigational device exemption application (IDE) or an investigational new drug application (IND), recommendations about certain information that should be included in a submission describing 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 cartilage repair or replacement products,[1] may include a biologic, device, or combination product[2] whose components would individually be regulated by the Center for Devices and Radiological Health (CDRH) or the Center for Biologics Evaluation and Research (CBER).[3,4] This guidance finalizes the draft guidance of the same title dated July 2007.

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" dated May 1996, (Ref. 1)). For general information on IDEs and INDs, see http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/default.htm and

[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 a product composed of any combination of a drug and a device; a biological product and a device; a drug and a biological product; or a drug, device and a biological product. For the definition of the term "combination product," see Title 21 Code of Federal Regulations, Part 3 (21 CFR Part 3) at 21 CFR 3.2(e).

[3] Forward specific questions regarding product jurisdiction with respect to a combination product to the Office of Combination Products (OCP). You may call OCP at 301-796-8930 or email OCP at 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 at http://www.fda.gov/CombinationProducts. 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/Ps) regulated solely under section 361 of the Public Health Service Act (PHS Act) (42 U.S.C. 264) and 21 CFR Part 1271 are beyond the scope of this guidance.

http://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/InvestigationalNewDrugINDorDeviceExemptionIDEProcess/default.htm, respectively.

We, FDA, typically regard investigational devices for articular cartilage repair or replacement to be significant risk devices (see 21 CFR 812.3(m)(1)) (§ 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 application for an IDE (21 CFR 812.20). 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) (§ 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 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 CTGTAC meeting (Ref. 2) and May 15, 2009 CTGTAC meeting (Ref. 9).

III. PRODUCT DESCRIPTION

For products subject to the IDE submission requirements 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:

- A complete written description of the individual components and how any components interact either mechanically or chemically. See §§ 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 §§ 812.25(d) and 812.20(b)(2). Depending on the material, we may recommend biocompatibility testing, as described in section VI. of this document.
- A description of anticipated changes to the device. See §§ 812.25(d) and 812.20(b)(2).
- A list and description of all instruments (including trial components) unique to the implantation of the product, the material or voluntary material standard(s) to which they conform, and supporting engineering drawings or photographs of them. See

§§ 812.25(d) and 812.20(b)(2). You should provide evidence that the instrument materials are safe for limited contact with a breached surface, any instructions for assembly/disassembly (if applicable), and a statement regarding whether the instruments are re-usable or for single use only, and if re-usable, adequate instructions on cleaning and sterilizing the instruments.

Depending on the particular design of the product, additional information may be appropriate:

- 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.
- Products regulated under an IND must include a description of the product into the Chemistry, Manufacturing, and Controls (CMC) section of the IND submission per § 312.23(a)(7). Recommendations for application of these regulations to cellular and gene therapy products are provided in the CMC guidances listed below in section IV.B. of this document.

IV. MANUFACTURING AND CMC INFORMATION

A. Device Component

Under § 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 FDA guidance entitled, "Updated 510(k) Sterility Review Guidance K90-1; Final Guidance for Industry and FDA" dated August 2002 (Ref. 3).

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

Section 312.23(a)(7) directs the sponsor to provide manufacturing and CMC information commensurate with the phase of the investigation. In addition, the current good tissue practice requirements in 21 CFR Part 1271 establish processing requirements applicable to all HCT/Ps, including those under IND.

For a cellular or gene therapy product or cellular constituents of a combination product, we recommend that you refer to the following FDA guidances:

- "Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy" dated March 1998 (Ref. 4);
- "Guidance for FDA Reviewers and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs)" dated April 2008 (Ref. 5); and
- "Guidance for FDA Reviewers and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)" dated April 2008 (Ref. 6).

V. NONCLINICAL DATA CONSIDERATIONS

You should provide nonclinical data sufficient to establish scientific support for clinical investigation of your product, and to demonstrate an acceptable safety profile of your product prior to initiating a human clinical study (see § 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 anticipated performance and address the safety issues raised by your product. The type of studies will be dependent on the exact constituents of your product. We encourage you to contact us about general and nonclinical testing to further define specific test recommendations. We recommend you 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.

While a description and analysis of the individual components of a product consisting of multiple components is necessary, it is not sufficient as it does not provide information on how the final product functions and the interactions in vivo. Because of this, the key nonclinical studies should ideally evaluate a version of the product that is identical to the product that is intended to be used in the clinical evaluations. If this is not possible, you should provide a rationale that addresses the differences between the various versions of the product and why the nonclinical data resulting from an analysis of a different product is applicable in support of initiation of clinical studies. In order to facilitate an appropriate review of the investigational application, we suggest that you provide information on the various versions of your product in tabular form that includes which nonclinical studies were conducted on each version, and where the study results are located in the IND or IDE submission.

A. Animal Data and Testing Considerations

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

- **Biological response** to the product and the 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** (length of time needed to assess repair of the cartilage lesion and the ability of the product to resist wear, degradation, withstand physiological relevant loads over time, etc.). You can assess durability of the response in large animal studies. Generally, studies that are a minimum of one year in length are recommended to provide an adequate period for completion of healing. This duration is also generally sufficient to allow assessment of durability of the therapeutic response, and of the integrity of the product. The study duration may vary depending on the product characteristics, type, and amount of data available. For example a product that takes longer to degrade may require longer follow-up for adequate characterization of the degradation profile.
- **Toxicology** (potential for local and systemic toxicities due to a 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 or particle migration outside of the articular space. Potential for tumorigenicity or inappropriate differentiation of cellular products exists within or outside of the articular space.
- **Dose response** (e.g., material constituents, cell number, and other characteristics, which may affect lesion repair). Dose response can often best be assessed in large animal studies[5] as a result of anatomic and biomechanical considerations.
- **Lesion size and location** evaluated in the animal study should be scaled appropriately to mimic what will be studied clinically. If multiple devices will be used clinically, this should be considered in the animal study design. In addition, the lesion should be located in an analogous location in the animal study as intended for implantation in humans.
- **Appropriate endpoints** should be used to design your animal study to mirror your clinical study; please consider incorporating secondary clinical endpoints from section VII.D. of this document into your study design (e.g., histology).
- **Use of arthroscopic and/or magnetic resonance imaging (MRI) evaluations**. To reduce the number of animal sacrifices at each timepoint, it may be appropriate to provide interim arthroscopic assessments and/or MRI evaluations in the animal studies. At the time of each sacrifice, the mechanical integrity of the cartilage should be assessed along with gross examination.

Other important considerations for the animal study include:

1. Suitability of Animal Model(s)

We recognize that choosing and determining the suitability of 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):

[5] See ASTM standard F2451-05 (Reapproved 2010) "Standard Guide for in vivo Assessment of Implantable Devices Intended to Repair or Regenerate Articular Cartilage." http://www.astm.org/Standards/F2451.htm.

- 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.

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 ASTM F2451-05, "Standard Guide for in vivo Assessment of Implantable Devices Intended to Repair or Regenerate Articular Cartilage," reapproved by ASTM in 2010.[6] This standard provides guidelines related to the development of animal models and mechanical testing. 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 (joint size and load, age, skeletal maturity);
- articular cartilage defect types (location, size, type, depth, etc.); 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.

Any of the large animal species referenced above 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 and provide a rationale for the animal model selected for your nonclinical study(ies) within your original IDE or IND application submission.

We further 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. It may be possible to utilize a combination of small and large animal studies to evaluate degradation, durability, safety, and efficacy.

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

[6] The standard is available at http://www.astm.org/Standards/F2451.htm or contact ASTM Customer Service at service@astm.org.

products are cellular products derived from the animal species used for testing that are analogs of the ultimate clinical product in cellular characteristics 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 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 FDA guidance entitled, "Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy" dated March 1998 (Ref. 4), and if applicable, the recommendations provided in section IV. of the FDA guidance entitled, "Guidance for Industry, Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events" dated November 2006 (Ref. 10).

2. Animal Report(s) to be Submitted

You should provide complete reports of any animal studies conducted using the investigational product[7], whether adverse or supportive, relevant to the evaluation of the safety or effectiveness of the investigational product. At a minimum, the following information should be included in the animal report:

- the purpose of the study;
- the rationale for the animal model used;
- a detailed methods section, to include the creation, size, and location of the cartilage defect;
- period of immobilization;
- reports on gait analysis;
- all tested parameters listed in section V. of this document, as applicable; and
- pathological, histological, and radiological evaluations.

In addition, you should explicitly describe any differences between the product used in the animal studies and the product proposed for clinical use in the IDE or IND.

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 (§ 312.23(a)(8)(iii) for INDs and § 812.27(b)(3) for IDEs). For

[7] Note that for IDE studies, sponsors must "include reports of all prior clinical, animal, and laboratory testing of the device" (21 CFR 812.27(a)). Note that for IND studies, sponsors must provide adequate information to support the basis for concluding that it is reasonably safe to conduct clinical investigations (21 CFR 312.23(a)(8)).

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 (§ 312.23(a)(8)(ii)(b)).

B. Mechanical Data and Testing Considerations

1. Suitability of Mechanical Testing

You should provide mechanical data for all articular cartilage repair or replacement products or a rationale addressing why limited mechanical testing coupled with complete animal study data are appropriate 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 indication for use.

Generally, the mechanical testing results should address the following:

- ability of the implant to withstand expected in vivo static and dynamic loading (e.g., compression, shear, and tension);
- analysis of fixation method (e.g., strength of integration between the product and surrounding native tissue); and
- propensity to generate wear debris.

Specifically, we recommend that you assess both the static mechanical behavior of the product by measuring the maximum recoverable compressive strain, the aggregate modulus (H_A), the shear modulus (μ), and permeability (κ) as well as the dynamic mechanical behavior of the product including an assessment of the complex shear modulus G*. These assessments of the mechanical properties should include a determination of any relevant anisotropies and nonlinearities in your product. In addition, you should determine the failure properties of your product. For products that contain a degradable scaffold component(s), it will be important to assess the failure properties as a function of time. Many mechanical testing methods may be used to measure the mechanical properties of your product, including, but not limited to, confined or unconfined compression and indentation. We recommend that you consult with FDA to discuss the appropriate mechanical testing methodology for your product as well as refer to ASTM F2451-05 (reapproved 2010) for additional information regarding test methods.

2. Mechanical Testing Report(s) to be Submitted

You should provide complete reports of any mechanical testing conducted on the investigational product[8], whether adverse or supportive, that is 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;
- description of the apparatus used;
- description of the procedures;
- rationale supporting the testing environment as being a worst case condition;
- rationale for the loading modes chosen;
- study results; and
- 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, and include an assessment of the degree of cartilage breakdown. This may be done visually after staining with India ink.

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 and ultimately form a load-bearing tissue). For these products, it would be appropriate to characterize various mechanical properties at discrete time points following maturation in a suitable animal model. You should initially assess the product's ability to maintain its location within the loaded joint (analysis of fixation or interfacial strength), and subsequently continue to assess this characteristic while adding assessments of the newly-formed tissue aimed to determine its ability to bear applied loads. Samples for these tests may consist of explanted regenerated tissue from the animal model or other appropriate samples as justified by the sponsor. 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.

[8] As previously noted, for IDE studies, sponsors must "include reports of all prior clinical, animal, and laboratory testing of the device" (21 CFR 812.27(a)). Note that for IND studies, sponsors must provide adequate information to support the basis for concluding that it is reasonably safe to conduct clinical investigations (21 CFR 312.23(a)(8)).

VI. BIOCOMPATIBILITY TESTING

Depending on the material(s) used in the product, we may recommend biocompatibility testing. According to ISO-10993, "Use of International Standard ISO-10993-1:2009, 'Biological Evaluation of Medical Devices Part-1: Evaluation and Testing'" (Ref. 7) and/or ASTM F748-06, "Standard Practice for Selecting Generic Biological Test Methods for Materials and Devices"[9] may provide 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.

VII. CLINICAL STUDY PROTOCOLS

Clinical studies of articular cartilage repair or replacement products must be conducted in compliance with the IDE regulations, which include requirements to obtain FDA approval for studies of significant risk devices (21 CFR Part 812) or the IND regulations (21 CFR Part 312), as appropriate, as well as with the regulations as to informed consent (21 CFR Part 50) and the regulations as to IRBs (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 early phase and phase 3 or pivotal clinical studies[10]. The number of clinical studies as well as the specific design requirements is contingent upon multiple factors, including the characteristics of the investigational product, the route of product administration (e.g., implantation), the characteristics of the target population, and the proposed product indication. This guidance provides only a broad outline of the major features to consider in designing a clinical study.

1. Early Phase Clinical Studies

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

- safety data (e.g., adverse experience reports, explant analyses where appropriate, revision procedure details);

[9] http://www.astm.org/Standards/F748.htm.

[10] "Exploratory", "feasibility", "phase 1", and "phase 2", are all terms that have been used to modify "clinical trials" in various situations to describe "early phase" clinical trials. Likewise "phase 3" and "pivotal" have been used to refer to "late phase" clinical trials. In an effort to increase simplicity, clarity, and readability, we will use "early phase" to denote all early phase clinical studies or trials, and we will use the phrase "phase 3 or pivotal" in this guidance to denote all late phase clinical studies or trials.

- data assessing the ability to properly implant the product, including identification of any study procedures (including surgical procedure) that should be modified to optimize product administration/implantation;
- bioactivity data, such as assessments of cartilage integrity based upon imaging results and/or biopsy findings;
- data assessing the appropriateness of the target 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; and
    - product design-response characteristics.

You should comprehensively evaluate early phase clinical study data to facilitate the design of phase 3 or pivotal studies. At the conclusion of early phase clinical studies, you should be able to provide clinical data explaining the important aspects of the phase 3 or pivotal clinical studies that apply to the investigational product, such as:

- data that support the product dose and design characteristics;
- route of administration, including surgical implantation 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 early phase clinical study of knee cartilage repair or replacement products is the potential use of a control group(s) to optimize the interpretation of the early phase 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 in early phase studies 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 to support phase 3 or pivotal clinical studies (for a more general discussion of controls groups in clinical studies of the products described in this guidance see section VII.B. of this document below).

2. Phase 3 or Pivotal Clinical Studies

Phase 3 or pivotal 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 require sample sizes larger than one might estimate based solely upon the projected primary

efficacy endpoint treatment effect. Consequently, we recommend that you consider both efficacy and safety considerations in designing phase 3 or pivotal clinical studies.

Typically, phase 3 or pivotal clinical studies use a randomized, controlled design. Whenever possible, we recommend that you use such a study design with endpoints ascertained in a blinded manner (e.g., subjects are blinded to treatment group, primary endpoints should be assessed in either a completely blinded manner or with the use of major endpoint evaluators who are blinded to the study treatment assignments). However, alternative phase 3 or pivotal study designs may be considered.[11] You should provide FDA with data (from your studies and applicable literature) and a rationale to support your phase 3 or pivotal study design prior to initiation of a phase 3 or pivotal study for any cartilage repair product.

We believe that the clinical knowledge base generated for current potential active concurrent controls (such as microfracture) has not established a treatment effect size with precision sufficient to employ a non-inferiority trial design. Therefore, we think that phase 3 or pivotal trials for these products should be designed and powered as superiority trials.

Listed below in sections VII.B through G of this document, are important considerations for the design of both early phase and phase 3 or pivotal clinical studies.

B. Control Group

Multiple options exist for the choice of a study's control group(s), and we recommend that you review the FDA guidance entitled, "Guidance for Industry: E 10 Choice of Control Group and Related Issues in Clinical Trials" dated May 2001 (Ref. 8). This guidance, while intended for biological products and drugs, contains concepts we believe may also be relevant to the clinical study of an investigational device intended for the repair or replacement of knee articular cartilage.

In general, control groups may be broadly classified as either concurrent or historical. 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 insufficient for phase 3 or pivotal 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

[11] For cellular and gene therapy, and combination products regulated under section 351 of the PHS Act (42 U.S.C. 262), please refer to the discussion of surrogate endpoints in the FDA guidance entitled, "Guidance for Industry on Fast Track Drug Development Programs: Designation, Development, and Application Review" dated January 2006 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079736.pdf.

standard treatment for the indication. For example, the 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. You should provide a rationale for the selected comparator(s). This rationale should include the comparability of the investigational 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.

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. Study Population

We recommend you pre-specify the following subject selection characteristics within a study protocol's eligibility criteria:

- age;
- degree of pain;
- presence or absence of osteoarthritis and method of diagnosis of osteoarthritis;
- chronicity of lesion;
- 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; and an assessment of general health status.

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.[12] You should provide a scientific rationale in your study protocol or supportive documents for selecting minimum values, maximal values, lesion depth, lesion size, and number of product(s) to

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

be implanted. To determine subject eligibility by clinical parameters such as pain and clinical function, we recommend that you use an established, validated clinical measurement instrument such as those described in section VII.D.

D. Study Efficacy 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 (e.g., implantation).

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 physical functioning as the primary endpoint for phase 3 or pivotal clinical studies. Examples of measures that may be used to assess these endpoints include the:

- Knee Injury and Osteoarthritis Outcome Score (KOOS)[13];
- IKDC Subjective Knee Evaluation Form-2000;
- Cincinnati Knee Rating System;
- Symptom Rating Form; and
- Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).

However, none of the above single validated instruments can be used to measure both joint pain and function. Therefore, separate validated instruments are recommended for measurement of both joint pain and function (Ref. 10). If you use a co-primary endpoint approach, then statistical success should be met by both endpoints in a manner that preserves the overall type 1 error.

Secondary endpoints that may be studied include:

- arthroscopic evaluation to assess:
    - 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.
    - the integrity of repaired tissue; and
    - the binding of implanted investigational product to adjacent tissue, including assessments of stiffness/firmness based upon tissue probing.
- assessment of the physical findings from examination of the knee joint, including:
    - both passive and active range of motion;
    - quadriceps muscle strength;
    - alignment;
    - degree of patellar subluxation;

[13] This form is available from http://www.koos.nu/.

  - degree of effusion;
  - degree of crepitus; and
  - degree of ligament laxity.
- 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);
  - collagen types and concentration;
  - aggrecan concentration, size, and composition;
  - other proteoglycan concentrations;
  - noncollagenous protein concentrations; and
  - 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 MRI, for:
  - articular surface integrity;
  - thickness and volume of chondral surface;
  - subchondral bone plate contour;
  - thickness and volume of synovial membrane; and
  - 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 with a third available for adjudication, if necessary. A core facility to interpret images independently could also be considered. 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 Implantation Procedures

The clinical protocol and supportive documents must provide a detailed description of the procedures to be used in implantation of the investigational product (§§ 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 implantation procedures. Any unique procedures for implantation 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, the use of antibiotics and pain medications, and the maximum number of product(s) that may be implanted, 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. If it is not possible to standardize the surgical technique or post-operative care regimen, all attempts to mitigate the potential introduction of bias and influence on the outcomes should be taken.

F. Follow-Up

You should include sufficient follow-up information from your clinical study for all investigational products within a premarket approval application (PMA) or biologics license application (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, and the natural history of the underlying target clinical condition. We recommend a minimum of two-year follow-up clinical information (subject to the degradation profile of the product) be submitted with the PMA or BLA. 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 early phase studies should continue to be followed during the period of phase 3 or pivotal studies or longer to provide some long-term follow-up information, which may be required as part of post-market surveillance, with a minimum of five years of follow-up.[14]

G. Adverse Experience (Risk) Reporting

This section concerns adverse experience (AE) reporting by the investigator(s) to the sponsor (§§ 312.64 and 812.150(a)(1)).[15] When an investigator reports AEs to the sponsor, 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 intervention, investigational product-related or not, should be reported and recorded.

[14] Characteristics of individual products may result in the need for longer than typical follow-up, such as gene therapy products as described in Reference 10.

[15] For requirements regarding AE reporting by a sponsor to FDA, see §§ 312.32 and 812.150(b)(1).

For the purpose of this guidance, 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, revision, modification, or addition of any component(s) to the product.

VIII. REFERENCES

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