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GUIDANCE DOCUMENT FOR THE PREPARATION OF INVESTIGATIONAL DEVICE EXEMPTIONS AND PREMARKET APPROVAL APPLICATIONS FOR INTRA-ARTICULAR PROSTHETIC KNEE LIGAMENT DEVICES

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This guidance document may contain references to addresses and telephone numbers that are now obsolete. The following contact information is to be used instead:

- **While this guidance document represents a final document, comments and suggestions may be submitted at any time for Agency consideration to the Orthopedic Devices Branch, 9200 Corporate Blvd., HFZ-410, Rockville, MD 20850.**
- **For questions regarding the use or interpretation of this guidance, contact the Orthopedic Devices Branch at 301-594-2036.**
- **To contact the Division of Small Manufacturers Assistance (DSMA), call 800-638-2041 or 301-443-6597; fax 301-443-8818; email dsmo@cdrh.fda.gov; or write to DSMA (HFZ-200), Food and Drug Administration, 1350 Piccard Drive, Rockville, Maryland 20850-4307. FACTS-ON-DEMAND (800-899-0381 or 301-827-0111) and the World Wide Web (CDRH home page: <http://www.fda.gov/cdrh/index.html>) also provide easy access to the latest information and operating policies and procedures.**

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Food and Drug Administration
Center for Devices and Radiological Health
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PREFACE

The development of a guidance document for intra-articular prosthetic knee ligament devices is based on the Division of General and Restorative Devices' (DGRD's) evaluation of numerous devices and the recognition of certain criteria necessary to conduct these evaluations. The purpose of this document is to suggest to the device manufacturer or investigation sponsor important preclinical and clinical tests that should be performed to generate data that will provide reasonable assurance of the safety and effectiveness of these devices for their intended purposes. Suggestions and recommendations written in the document are not mandatory requirements. They reflect methodologies which DGRD has determined to be acceptable and which, if followed, will assure well designed and scientifically valid Investigational Device Exemption (IDE) and Premarket Approval (PMA) applications. In this context several points should be remembered:

1. The guidance document is primarily intended to be a scientific position paper. Therefore, it suggests some important evaluation criteria, test procedures, and end points. If the same objectives can be achieved by other means, the investigator should not refrain from doing so.
2. The guidance document should be viewed as a living document. As science changes and scientific techniques are improved, FDA will periodically revise the document. Nonetheless, it should be remembered that the basic objectives may remain the same.
3. The word "should" and "must" have been used frequently in this document to emphasize the relative merit or importance of a specific aspect of a test or protocol. However, this verbiage is not used in a regulatory sense and should not be construed as such.

Guidance document preparation was initiated by DSRD (DGRD was formerly known as Division of Surgical and Rehabilitation Devices (DSRD)) staff Karen L. Goldenthal, M.D., Janet Guerrin, M.S., and Nirmal K. Mishra, Ph.D., D.V.M., in December of 1985 following a history of activity in the field including a meeting of the Orthopedic and Rehabilitation Devices Panel to discuss prosthetic ligament devices in November, 1983. In May of 1986, DSRD completed a first draft of the document containing preclinical and clinical testing recommendations and suggestions for the preparation of IDEs and PMAs. It was intended that the document be reviewed by Panel members with public comment at the June 19 and 20, 1986 Panel meeting so that the draft could be revised and made available for public comment. The industry representative to the Panel requested that the discussion be postponed until he could receive comments from his constituents. HIMA undertook the task of soliciting comments from industry and provided these to DSRD shortly before the October 31, 1986 Panel meeting. At this meeting, an open public session preceded the discussion of the document by the Panel. As a result of the October 31, 1986 Panel meeting, two working groups were established based on nominations from the Panel and industry:

Working Group for Evaluating Mechanical Test Recommendations:

Chairman (designated by Panel) - Savio Woo, Ph.D.
FDA Liaison - Janet Guerrin, M.S.
FDA Liaison - Daniel Chwirut, M.S., ~P.E.
Panel Member - A. Seth Greenwald, D. Phil(Oxon)

Panel Member - Peter A. Torzilli, Ph.D.
HIMA Representative - William C. Bruchman, B.S.
OSMA Representative - Walter P. Spires, Jr., M.S.

Working Group for Evaluating Biological Test Recommendations:

FDA Liaison - Nirmal Mishra, Ph.D., D.V.M.
HIMA/OSMA Representative - Vince Mendenhall, Ph.D., D.V.M.
HIMA/OSMA Representative - John Willson, Ph.D.

Working groups reviewed draft document recommendations which were revised according to Panel member comments, HIMA comments, and OSMA comments. After meeting with both working groups, DSRD again revised the document and accepted further comments from the working groups. The final draft of the document was then reviewed by the following Panel members and consultants at the May 7, 1987 Panel meeting:

Kenneth E. DeHaven, M.D.
Victor J. Ferrans, M.D., Ph.D.
A. Seth Greenwald, D. Phil(Oxon)
F. Joseph Halcomb, M.D.
Randall J. Lewis, M.D.
Michael B. Mayor, M.D. (Chairman)
M. Clinton Miller, III, Ph.D.
Kurt M.W. Niemann, M.D.
Eric L. Radin, M.D.
Kenneth M. Singer, M.D.
Peter A. Torzilli, Ph.D.
Bertram Zarins, M.D.

The Orthopedic and Rehabilitation Devices Panel voted unanimously to endorse the document with several changes at the May 7, 1987 Panel meeting. This document incorporates the changes. According to recommendations made by industry groups and the Panel this document would be reviewed again in 1 year at a meeting of the Orthopedic and Rehabilitation Devices Panel. Revisions would be made according to comments voiced by the public and the Panel at that meeting. The document would be reviewed and revised, if necessary, every 2 years thereafter.

After the May 7, 1987 Panel meeting and the document was finalized on September 1, 1987, there were no further formal discussions of this document. This document has been used by many in industry for conducting new studies with ligaments and has been well received. Since its introduction, several new ligaments have been approved for market bringing the current number of approved ligaments in the U.S. to three. The three approved ligaments are the Gore-Tex™ Cruciate Ligament Prosthesis by W.L. Gore and Associates approved on October 10, 1986, the Stryker® Dacrone Ligament Prosthesis by Meadox Medicals, Inc. approved on December 30, 1988 and the 3M Kennedy LAD™ Ligament Augmentation Device by 3M which was first approved on May 7, 1987 for the Marshall-MacIntosh procedure and then the indication was expanded on December 31, 1992 to include the use of the patellar tendon graft of 10 mm or smaller in patients more than 3 weeks since injury. The Summaries of Safety and Effectiveness for these devices can be obtained from the FDA Freedom of Information Office at 5600 Fisher Lane, HFI-35, Rockville, Maryland 20857 to obtain examples of preclinical and clinical work necessary for FDA approval.

INTRODUCTION

Purpose

It has been determined by the Food and Drug Administration (FDA) that all intra-articular prosthetic ligament devices are post-amendment significant risk devices. Therefore, an investigational device exemption (IDE) application is required prior to the start of clinical trials and a premarket approval (PMA) application is required prior to marketing these devices. It is the purpose of this document to aid in the preparation of IDEs and PMAs for intra-articular prosthetic knee ligament devices. Specifically, this document is intended to inform the device manufacturer or investigation sponsor (hereinafter referred to as the sponsor) of the preclinical and clinical testing that should be performed to generate data that will provide reasonable assurance of the safety and effectiveness of these devices for their intended use. Due to the critical nature of anterior cruciate ligament (ACL) and posterior cruciate ligament (PCL) injuries and because of their strenuous loading and harsh environment, this document is concerned with ACL and PCL prosthetic devices rather than prosthetic knee ligament devices in general. However, it is believed that the following requirements and suggestions will be applicable to all such devices. The Division of General and Restorative Devices (DGRD) of the Office of Device Evaluation, Center for Devices and Radiological Health (CDRH), may be consulted prior to the initiation of any tests and the submission of an IDE in order to discuss recommendations or specific requirements for a particular device.

Structure

The document consists of two sections: preclinical and clinical. The preclinical section includes suggestions and requirements for physical and chemical analyses-, biological tests, sterilization and stability, mechanical tests, and long-term animal studies. The clinical section includes FDA definitions and suggestions and requirements for clinical protocol and the presentation of clinical data.

Authority

While use of this document to prepare preclinical and clinical protocols will not ensure IDE or PMA approval, following the document will ensure that necessary tests are conducted to enable FDA to determine whether or not an application is approvable. Approval can be expected to follow if tests are conducted properly, data are adequately analyzed and presented, and the test results support a conclusion that there is reasonable assurance that the device is safe and effective for its intended use. Use of the procedures that differ from those outlined in the document require that the applicant demonstrate to FDA that such procedures provide the requisite reasonable assurance of device safety and effectiveness.

Pertinent Regulations

FDA regulations relevant to this document can be found in the Code of Federal Regulation Title 21 (21 CFR):

General Information

- Determination of Safety and Effectiveness (defines valid scientific evidence) (21 CFR 860.7)
- Environmental Impact Considerations (21 CFR 25)

Investigational Devices

- Protection of Human Subjects; Informed Consent (21 CFR 50)
- Standards for Institutional Review Boards for Clinical Investigations (21 CFR 56)
- Good Laboratory Practice (GLP) Regulations (21 CFR 58)
- Investigational Device Exemptions (21 CFR 812)

Premarket Approval Devices

- Premarket Approval Application procedural regulation (Federal Register, July 22, 1986) and "Premarket Approval (PMA) Manual", October, 1986
- Medical Device Reporting (21 CFR 803)
- Premarket Approval of Medical Devices (21 CFR 814)
- Good Manufacturing Practice (GMP) for Medical Device General (21 CFR 820)

Types of Devices

CDRH recognizes two basic types of intra-articular prosthetic knee ligament devices. These are: 1) devices intended as frank replacements and 2) devices intended to augment natural tissue. The augmentation type devices include a broad category of prostheses with diverse functions such as prostheses which act as a scaffold for tissue ingrowth, prostheses which give mechanical support to autogenous reconstruction procedures, prostheses which resorb or degrade with time and are intended to be replaced with ingrown host tissue, and other prostheses whose function is dependent on tissue ingrowth or mechanical support from autogenous structures.

Preclinical and clinical protocols for these two device types will vary according to differences in materials, intended function, and risk-benefit considerations. It must also be recognized that frank replacement and augmentation type devices made of heterograft will have different risk-benefit considerations. At this time, CDRH does not regulate the use of allograft tissue for ligament reconstruction.

Abbreviations Used in the Document

Anatomic terms: Anterior cruciate ligament (ACL), posterior cruciate ligament (PCL), medial collateral ligament (MCL), lateral collateral ligament (LCL)

Administrative terms: Division of General and Rehabilitation Devices (DGRD), Center for Devices and Radiological Health (CDRH), Food and Drug Administration (FDA), Investigational Device Exemption (IDE), Premarket Approval Application (PMA), Investigational Review Board (IRB)

PRECLINICAL RECOMMENDATIONS

Introduction

The purpose of the preclinical section of the document is to assist the sponsor in developing adequate preclinical protocols and testing procedures to demonstrate the safety and effectiveness of intra-articular prosthetic knee ligaments.

The preclinical data should include a comprehensive description of the device. The sponsor should clearly list the device components and materials and state whether or not any have been used previously for human implantation, and, if so, list these components and/or materials. For frequently used materials, several examples of previous use will suffice. If the material has not been used for human implantation, but has industrial uses, these uses should be stated and any adverse data concerning the effect on animals or the environment must be provided to CDRH.

The requirements for preclinical testing will be influenced by the type of material, the type of prosthesis, and previous use of the material in humans. For example, processed products of biological origin will require extensive immunological testing. If a material degrades, then the fate of the material in the body or joint must be determined. Consultation should be made at an early stage with DGRD to determine what preclinical tests are appropriate.

A comprehensive summary of all preclinical testing should be included in addition to specific detailed test descriptions. For each test, the sponsor should detail the test procedures including equipment, protocol, measurement techniques, and test parameters. Test descriptions should clearly state what component of the device is being tested. The consequences of test results should be discussed in terms of the expected in-vivo performance of the device in the human knee.

In general, CDRH requires that all preclinical test data must be provided before an IDE can be approved prior to the initiation of a clinical trial. The sponsor must state whether or not all preclinical safety tests were performed in compliance with GLP, 21 CFR Part 58. The GLP regulation is limited to safety studies, i.e., those which can be used to predict adverse effects of, and to establish safe use characteristics for a regulated product. Functionality studies are excluded. However, all nonclinical tests should be conducted according to good scientific practice.

PHYSICAL AND CHEMICAL ANALYSES

These procedures are intended to supplement biological testing and are required for all device types. The first objective of physical and chemical analyses is to identify and characterize the device in its entirety. If the device is claimed to be reasonably comparable to devices described in literature, then these tests can be used to demonstrate that data from the literature can be extrapolated in support of the investigational device safety.

The objective of these analyses is also to identify leachable materials per unit weight of finished device material under exhaustive extraction conditions. At present, it is suggested that at least two solvents (one polar, one non-polar) be used for extraction at elevated temperatures (37°C, for 5 days) in a ratio of 1 gm of synthetic polymer (shredded, if possible, to maximize surface/wt)

per 5 milliliters (ml) of extraction media, according to ASTM F619. It is suggested that the extracts should then be re-extracted with a compatible solvent, such as methylene chloride or tetrahydrofuran, to a minimum possible volume in order to achieve maximum sensitivity of the analytic technique. When possible, and where a potentially leachable substance is known, calibration standards should be prepared and the concentration of the substance in the extract should be calculated using suitable analytical techniques (GC, HPLC, etc.). For processed materials of biological origin, the extraction process may be tailored to identify the extraneous processing agents in an optimal fashion, e.g., cross-linking chemicals.

Identification of the extracted material should be performed on extracts concentrated to a convenient volume. CDRH recommends that a sensitive procedure such as gas chromatography be used in conjunction with mass spectroscopic Analysis for identification of separated peaks. However, other validated, sensitive analytic methods may also be used.

BIOLOGICAL TESTING

The objective of pre-clinical biologic testing is to establish that the material and processing used to fabricate the device do not present adverse toxicological effects. The ultimate goal of these tests is to ensure that the final device does not impose undue risk to the patient. If the material has prior clinical usage history, many conclusions regarding device safety can be made by reviewing such data. Similarly, toxicological information, particularly component toxicology and pharmacokinetic information, can often be obtained from a careful literature search. It should be noted, that in order to use data taken from the literature, the sponsor must establish that the chemical and physical characteristics of the investigational device, including the process residuals, are reasonably comparable to those of the device found in the literature.

The following tests describe methods of worst-case determinations used to identify toxic substances. The results of these tests, the so called "hazard identification information," should be provided. It should be realized that "hazard parameters" are generally utilized in accordance with basic tenants of toxicology and consist of three distinct phases: identifying the hazard, extrapolating from the dose given to obtain a risk estimate, and evaluating the risk compared to the benefit of the use of the substance. All testing procedures must conform to acceptable toxicological principles such as exaggerated dose/response criteria and statistical validity of data.

Pyrogenicity Testing

The goal of pyrogenicity testing is to determine the presence of fever-producing substances. For most devices, it may be appropriate to conduct a USP rabbit test on a saline extract of the device to demonstrate device safety preclinically. An in-vitro limulus amebocyte lysate (LAL) assay, for bacterial endotoxin detection, should be conducted as an end-product test for quality assurance. However, for biological materials, both USP rabbit tests and LAL assays should be conducted and reported in the IDE as part of the preclinical safety testing.

The pyrogen test and the LAL assay should be performed with the sterilized device saline extract. The test extract should be prepared at elevated temperatures (37-40°C) using a high surface area to solution ratio. Additionally, other methods such as sonication may be used. For the LAL

assay, appropriate sensitivity and inhibition/enhancement tests should also be performed concurrently, and all results should be expressed in standardized units (nanograms or standard units of endotoxin per unit weight of the device).

Hemolytic Potential

Contact tests or saline extract, tests should be used for determining the hemolytic potential of the device or material. Any standard protocol which uses spectrophotometric analysis for hemoglobin may be used. CDRH recommends using the "Standard Practice for Assessment of Hemolytic Properties of Materials", ASTM F756.

Acute Toxicity And Intracutaneous Irritation Testing

Acute toxicity and intracutaneous irritation tests should be conducted using extracts prepared according to USP. One polar and one non-polar solvent, such as water or saline and cottonseed or sesame oil should be evaluated. Two tests should be performed: a USP systemic injection test, and a USP intracutaneous test.

Cytotoxicity Testing

An appropriate cell line such as L929 mouse fibroblasts should be exposed to the device material and to both the polar and nonpolar USP extracts of the intact device. It may be appropriate to expose the cell lines to a DMSO extract in addition to an aqueous extract. It should be noted that DMSO should be used at concentrations below 5% to prevent toxicity to the cell culture. The basic purpose of these tests are to detect soluble leachables (primarily low-molecular weight chemicals) during early investigations.

1. Agar diffusion test (Toxicological Evaluation of Biomaterials, 1977); an in-vitro assay that measures the toxic response of the device in L929 mouse fibroblasts. The assay is designed to detect toxic water soluble and diffusionable entities in the product. In addition to agar diffusion tests, the sponsor should attempt to conduct direct contact and/or water or minimal essential medium (MEM) elution tests.
2. Direct testing for cytotoxicity. CDRH recommends that the USP extracts be tested for cytolethality by comparing colony forming ability (colony suppression assay) and growth pattern changes at low cellular plating densities. These are simple, inexpensive tests in which the cell division time parameters and the ability of individual cells to establish colonies are measured in both control and treated groups.

Genetic Toxicity Testing

It is recommended that the battery of tests listed below be performed on a minimum of two extracts, one polar solvent and one non-polar solvent. When evaluating data from this test battery, equal weight is assigned to each system without preferential weight given to any

particular system. Substitutions of other accepted genetic toxicity tests may be made for those listed below. The sponsor should give justification for any variation in the tests performed.

1. Ames/Salmonella Assay (Methods for Detecting Carcinogens and Mutagens, 1977). This assay should be performed with and without metabolic activation in Salmonella strains TA1535, TA1537, TA1538, TA98, and TA100.
2. Mammalian Mutagenesis Assay (Laboratory Procedures for Assessing Specific Locus Mutations, 1975, and Utilization of a Quantitative Mammalian Cell Mutation System, 1979). Two mammalian mutagenesis systems are recommended. These are the L5178Y/TK \pm assay and the CHO/HGPRT assay. Both systems utilize mammalian cells in culture and are believed to detect forward mutations at the thymidine kinase (TK) locus in L5178Y mouse lymphoma cells or the hypoxanthine guanine phosphoribosyl transferase (HGPRT) locus in Chinese hamster ovary cells (CHO). Both systems have been demonstrated to identify both base pair substitution type and-frame shift type mutagens. Any one of the above assay systems are acceptable to CDRH.
3. Mammalian cell transformation assay (Cell Transformation by Chemical Agents, 1983). This is the only in-vitro. assay that may detect a carcinogenic response, i.e., transformation of a normal cell to a malignant cell. Two systems are recommended, C3H/10T1/2 assay and Ba1b/C3T3. Any one of the above assay systems is acceptable to CDRH.
4. Unscheduled DNA synthesis in primary rat hepatocytes (UDS Assay) (Unscheduled DNA Synthesis Tests, 1983). This is an assay system that can detect damage produced to molecular DNA in cultures of primary rat hepatocytes. A positive response indicates potential mutagenic or carcinogenic properties of the test material since the damage detected is to the genetic material of the cell.

Immunological Potential Testing

The biomaterial used for the fabrication of the ligament should be evaluated for delayed-type contact sensitization potential by a suitable method (Dermal and Eye Toxicity Tests, 1977).

Immunologic studies other than contact sensitization studies are not required for synthetic polymers. However, if the ligament is fabricated from materials of biological origin (e.g., processed heterograft) extensive preclinical testing should be performed in suitable models, such as the rabbit and guinea pig. These studies should be directed to establish the quantitative biologic response toward the device material. A sensitive test procedure for circulating antibody response (e.g., competition radioimmune assay or ELISA assay) and for cell-mediated immune response should be utilized. Careful documentation must also be made for histological studies in device implantation studies in terms of immune response. CDRH recommends that special staining techniques be used in addition to standard histological staining.

STERILIZATION AND STABILITY

Sterility information for devices and their packaging must be included in the description of manufacturing in IDEs and PMAs. In addition, devices of biological origin should be tested preclinically to validate the sterilization process and to demonstrate that the process does not have a deleterious effect on the biological or mechanical properties of the device.

For devices of biological origin, the method and details of the sterilization process and validation and bioburden level data must be submitted in an IDE. These should conform to AAMI guidelines. Validation data should include mechanical testing performed on the sterilized device. Products sterilized by ethylene oxide gas must be analyzed to determine residual EtO levels.

The shelf life of the sterilized device should also be stated. Data should be submitted which demonstrate that device properties are not compromised by prolonged storage.

For products not marketed sterile, labeling must recommend the method and details of the sterilization process. Data must be submitted to assure that the process will reasonably achieve the desired sterility levels.

MECHANICAL TESTING

The following mechanical tests should be conducted to assure acceptable strength, stiffness, elongation due to creep, and fatigue life. CDRH does not require that all tests be completed prior to submission of an IDE. However, there must be adequate data and information for CDRH to make a reasonable assumption concerning the safety and effectiveness of the device.

Tensile Testing

For all types of devices, the sponsor must determine the structural properties, and if possible, the material properties of the finished ligament prosthesis. Tensile testing should be conducted to failure in order to provide data as indicated in [Appendix 1](#). Mean load-deformation curves should be provided with standard deviations. where appropriate, mean stress-strain curves with standard deviations should be provided for the constituent material in order to characterize the material.

Tensile tests should be conducted on the finished device as manufactured in a preconditioned state. Preconditioning should involve the introduction of factors such as sterilization and preloading that are present prior to implantation of the device. Tests should be conducted at a minimum of three different strain rates representing slow to rapid loading (for example, 2%/sec to 100%/sec) in order to determine any strain rate dependency of the material. For tests of structural properties, grip configurations and gage lengths should simulate in-vivo loading conditions as closely as possible. If necessary, gage lengths less than that of in-vivo loading conditions may be used for rapid loading. Tests should be conducted at 37°C in a normal physiological fluid unless the material and structural properties are demonstrated to be independent of the effects of these variables. It may be appropriate to determine the effects of prolonged soaking in physiological solution and prolonged exposure to body temperature. A minimum of six devices should be tested at each strain rate.

Experimental and analytical techniques used for the measurement or calculation of load, stress, displacement, and strain should be described. Data for each test should be presented as a mean value with the standard deviation and coefficient of variance given. An in-depth discussion of the data should be provided which includes a comparison between the device properties and known properties of the human ligament in the population in which the device will be implanted.

Fatigue Testing

Fatigue testing must be conducted in order to determine the fatigue life of the device and the elongation due to creep. Fatigue life may be determined by developing a load-cycle curve and estimating the cycles to onset of rupture due to fatigue under simulated in-vivo conditions. Excessive elongation due to creep may also be a mode of failure and may be determined by developing an elongation-cycle curve and estimating the cycles to onset of rupture due to creep or excessive elongation. Both potential failure mechanisms should be characterized in this test. Data should be gathered and presented as shown in [Appendix 2](#).

Augmentation devices which are designed to degrade with time and which are not expected to retain any of their original properties in-vivo may be excluded from long-term tensile fatigue testing. For these devices, the intended function must be described in detail and demonstrated with animal data. The length of time the device is expected to carry a significant portion of the load imposed on the knee should be stated. Abbreviated tensile fatigue testing should be done as described below in which the fatigue life and elongation due to creep are determined within this time period. In addition data concerning in-vivo device strength reduction with time must be provided.

Tensile fatigue testing should be conducted on the finished device. Tests should be conducted in normal physiological fluids at 37°C unless the effects of prolonged exposure to fluids and temperatures generated during testing are known and accounted for in the calculation of device life. The cycling rate should be representative of normal activities. A justification for the choice of cycling rate should be provided including a demonstration that the rate is compatible with the testing machine, temperature effects, and material properties. The cycle profile should attempt to describe in-vivo loading.

Fatigue life should be established by determining the number of cycles to failure under cyclic peak loads ranging from high loads which will produce failure in less than one million cycles to low loads typical of normal activities. A minimum of three load levels should be used and justification should be provided for those chosen. A sufficient number of devices should be tested to characterize the variability of the material at each load level; it is suggested that six devices may be adequate. Fatigue data should be fit to a regression model in order to predict the number of cycles required to produce device failure at these loads. It is suggested that elongation be measured throughout the fatigue process. Permanent elongation due to creep should be determined as a function of cycles. An SN type curve and an elongation-cycle curve should be included. If failure does not occur by 1×10^7 cycles, fatigue tests may be discontinued. Total permanent elongation at zero load should be measured. The device should then be tested in tension to failure. Residual failure load and stiffness should be recorded.

A description of equipment, test protocol including cycle profile, and measurement techniques used for the determination of load and elongation due to creep, including any calculations, should be provided. The expected life of the device, in-vivo, under loading conditions endured by the population in which the device will be implanted should be presented. A discussion of the results should also include the significance of the device creep properties in terms of device performance. Static creep may be conducted in support of the tensile fatigue data.

Bending Fatigue Testing

For frank replacement type devices and most augmentation devices, bending fatigue tests must be conducted to demonstrate adequate bending fatigue life under conditions simulating in-vivo use. CDRH recognizes that there does not exist a standard for bending fatigue testing. However, there has been clinical evidence, with investigational devices, that bending and/or abrasion occurs and can be related to device failure. Therefore, careful consideration should be given to this potential mode of failure. CDRH suggests that the following test may provide valuable data for a worst case determination of device failure due to bending and/or fatigue. [Appendix 3](#) indicates the required data.

Bending tests should be conducted on the finished device. Tests should be conducted in normal physiological fluids, preferably at 37°C. CDRH suggests that a special purpose test apparatus be constructed in order to conduct tests with the device in bending. Tests should be conducted at three angles with a load typical of normal activity or at three loads with an angle representative of normal bending. The angle of bending should be representative of normal bending in-vivo and will vary depending upon the method of implantation, i.e., around bone tunnels or "over-the-top." However, CDRH recognizes that angles could be in excess of 90°. Tests should be conducted to failure or to 1×10^7 cycles. At the completion of the test, if rupture has not occurred permanent elongation, the residual failure load, elongation, and stiffness should be determined. A minimum of three devices should be tested at each load or angle, i.e., a total of nine samples.

A description of equipment, test protocol, and measurement techniques should be provided. The method used to produce bending, cycling rate and profile, and any calculations should be included. A discussion of the bend fatigue life of the device under conditions simulating in-vivo use should be given with conclusive data.

Fixation Strength

Testing must be conducted in order to determine the fixation anchorage strength and the potential for abrasion for the device. The ultimate tensile pull-out strength of the device from its attachment site should be determined under loading conditions simulating normal physiological conditions. If the ligament portion of the device attaches directly to bone or soft tissue, such that ingrowth is its primary mode of fixation, animal studies should be used to determine fixation strength as a function of implant time. Initial fixation, and fixation of devices not intended to have biological ingrowth at the attachment sites, can be tested without animal implantation. However, CDRH suggests using animal studies to evaluate device fixation no matter what type fixation is used.

In lieu of animal data, the device with the fixation system should be implanted and tested in cadaverous bone to demonstrate device safety with respect to fixation pull-out strength and fixation loosening. For devices whose primary mode of fixation is not by ingrowth, that is, through a non-biological fixator or interface between the ligament substrate and the bone or soft tissue attachment site, pull-out strength should be determined for (1) the entire device from its in-situ bone or soft tissue attachment site, (2) the ligament substrate itself from its fixator to bone or soft tissue, for example, staple, metal plug, cement, etc., and (3) the fixator itself from its bone or soft tissue attachment site. Ultimate pull-out strength and mode of failure should be reported.

Abrasion Testing

CDRH recognizes that failure due to abrasion and complications due to the release of particulate matter into the joint have been observed clinically with investigational devices. Therefore, careful consideration should be given to the potential of device abrasion. However, at this time, CDRH is not aware of a predictive mechanical test to measure this phenomenon. It is suggested that careful examination be made in animal studies and attempts be made to characterize the release of particulate. It may be appropriate upon finding evidence of particulate clinically, in a significant number of patients, to conduct mechanical abrasion tests. Abrasion tests could be performed by simulating physiological conditions for abrasion at the attachment sites and at other places along the device where rubbing on bone might occur. CDRH suggests utilizing cadaver bone, or, if not appropriate, different grades of abrasive material. While CDRH realizes that these tests will probably produce premature device failure, well before that occurring in actual use, the data will provide meaningful information for the prediction of wear life and particulate material accumulation. Attempts should be made to perform separate tests incorporated into the bending fatigue tests described above, with the purpose of characterizing particles generated due to abrasion and determining the maximum volume of particles that could be released.

LONG-TERM ANIMAL STUDIES

Device Implantation in Animal Stifles

Pre-clinical in-vivo testing should include chronic (1 year or more) device implantation in animal stifles in a loaded configuration to characterize the type and time course of the post-implantation biological and mechanical events. While CDRH realizes that the unique properties of the human knee, including its large range of motion, make it difficult to extrapolate data from an animal study in support of device effectiveness, much data can be obtained from such a study in support of device safety. Therefore, in-vivo test data will be relied on heavily as evidence of:

1. the histological reaction to the device and device particulate;
2. the immunological reaction to the device;
3. device material degradation leading to a loss of desired properties;
4. device abrasion and/or damage;
5. the migration of particulate matter; and
6. the strength of fixation.

CDRH may not require that all tests be completed prior to the submission of an IDE. However, there must be adequate test data and information for CDRH to make a reasonable assumption concerning the safety of the device as outlined above.

CDRH has not identified an ideal animal model which should be used for in-vivo testing. However, CDRH notes that studies conducted on sheep, goats and dogs have been successful. Animals should be determined to have closed epiphyses prior to study. The testing should include the same device and, preferably, the same fixation system intended for human application, although a different size may be necessary. Any difference between the device or fixation system used for human implantation versus that used for animal studies should be clarified by the sponsor.

Interim animal sacrifices should be scheduled to reflect the histological and mechanical response at acute and subchronic time points. CDRH recommends that evaluations be conducted at 3-months and 12-months post-implantation at a minimum. If pathology studies and mechanical tests are performed on separate groups of animals, then CDRH estimates that pathology studies on three control animals (sham operated) and three device implanted animals at an early and a late time point and mechanical tests on six animals at each time point, or 24 total animals, is the minimum study design that should be adequate. However, it should be noted that these are minimum recommendations and do not take into account the possible premature loss of animals. Careful consideration should be placed on the type of device and the purpose of the animal study particular to that device type. For example, investigators of devices intended to achieve tissue ingrowth must demonstrate the nature of ingrowth with animal studies and must demonstrate whether or not device strength is increasing with time due to ingrowth.

The surgical implantation technique and postoperative care should be described in detail. Specifics of the surgery such as graft isometry, measured graft tension and joint position at the time of graft fixation, as well as joint position with the limb immobilized should be discussed. Clinical evaluation of the stifle-stability and usage must be performed on all animals. A measure of clinical functionality and/or x-rays should be obtained from anesthetized animals for the purpose of suggesting effectiveness.

Pathology Studies

At sacrifice, each implanted stifle should be examined and described in detail and in situ photographs of the prosthesis and surrounding joint components should be taken, whether the stifle will be used for mechanical or histologic studies. For the pathology study animals, the gross and microscopic pathology of the tissue surrounding the device, the amount of fibrous ingrowth into the device, and the various joint components such as the menisci should be reported. Synovial fluid should be analyzed. Abraded particles in the joint should be evaluated for size distribution, quantity, and type of reaction elicited. Gross necropsy examinations should be conducted on all animals and conventional histologic studies of major organs (e.g., liver, kidney, lungs, spleen) should be performed. In addition, any areas of grossly evident pathology should be evaluated histologically. Lymph nodes, particularly regional lymph nodes, should be examined histologically in detail for migrated particulates. It may also be possible to examine the synovium and lymph nodes of mechanical test animals grossly and microscopically. Raw histological data in addition to summarized data should be submitted.

Mechanical Testing

At sacrifice, the device itself should be examined and the gross and, if possible, the microscopic findings should be described. The amount of fibrous ingrowth and any abraded or damaged material should be reported. Normal control ligament laxity should be documented with the ligament intact and after sectioning. Laxity should be measured after implantation of the device, and at sacrifice. Mechanical testing should be conducted on the entire device with the fixation system intact and on the intra-articular device material in order to test the ligament strength and the integrity of the attachment site as a function of time. If ingrowth is intended to supplement fixation strength, this must be

demonstrated in tensile tests with the initial fixation removed. The fixation strength and stiffness and the intra-articular material strength and stiffness of the device and normal control ligament should be compared at implantation and at sacrifice at various time intervals. A regression analysis of strength and stiffness versus implantation time should be provided for both the device and the normal control ligament.

Particulate Migration Studies

The purpose of particulate migration studies is to obtain worse-case information for possible future corroboration with clinical results. For devices in which abrasion may cause the release of material particles into the knee joint, preclinical in-vivo testing should include a study of the migration of particulate matter. The sponsor should estimate the worse case situation for intra-articular abraded particles and inject that amount of material into the joints of an appropriate animal model.

Detailed justification should be provided for the doses and size/geometry of the particles used. Some animals should be kept for a minimum of 1 year to estimate the long-term effects. The type of histologic reaction elicited by abraded particles, and the effect on intra-articular structures should be documented with gross and microscopic pathology. Regional lymph nodes of the animals should be examined for migration of particulate matter. CDRH notes that it may be appropriate to evaluate these data only in conjunction with the clinical results.

Carcinogenesis Bioassay

If the sponsor cannot demonstrate that the device materials) has been previously used for human implantation for a significant period of time, CDRH will consider it a new biomaterial. For all new implant materials, the carcinogenic risk to humans must be addressed. For a new biomaterial CDRH requires that a life-time (2 year) implant bioassay be performed. An IDE can be approved with an ongoing bioassay provided the results of the genetic toxicity battery are negative. However, a PMA cannot be approved without acceptable final results from the bioassay.

The bioassay should be performed as follows. The maximum implantable dose (MID) of the device should be implanted in the paravertebral muscle of rats. The MID should be expressed as a multiple of the actual "worse case" exposure with detailed justification of the calculation given. The MID may be introduced in either a solid or a ground/shredded form, again, with justification given for the chosen method. CDRH suggests that a ground/shredded material be used in order to maximize the available surface area and to minimize the possibility of solid-state carcinogenesis. Rats with a reasonable natural background occurrence of tumors, such as a Fischers, rat, should be chosen. There should be 100 animals (50 male and 50 female) receiving a suitable negative control material and 100 animals (50 male and 50 female) receiving the investigated implant material. Animals should be examined regularly. (Interim sacrifice can be made; however, at least 50 percent of the animals per sex, per group, should be available for final sacrifice.) Detailed gross pathology and microscopy must be presented on animals that die during the interim. Complete accounting and postmortem examination, with microscopic pathology, must be performed on all animals. In general, up-to-date methodologies and guidelines issued by the National Toxicology Program should be adhered to for all aspects of conducting the assay.

CLINICAL RECOMMENDATIONS

Introduction

The purpose of the clinical section of the document is to assist the sponsor in developing an adequate protocol for use during the clinical investigation of prosthetic intra-articular knee ligaments and in presenting the data obtained from this investigation. The clinical protocol is part of the investigational plan that must be presented to an IRB and CDRH to give reasonable assurance that the clinical trial conducted under the IDE will accrue useful information. The data obtained under the IDE must be presented in order to establish reasonable assurance of device safety and effectiveness and subsequently to obtain PMA approval. Part 812.25 of 21 CFR and "Premarket Approval (PMA) Manual" include the required elements of an investigational plan and the required clinical data to be included in an IDE and PMA, respectively.

The IDE investigational plan should state the purpose for the study. The protocol should clearly list the major study characteristics (number of patients, number of investigators, number of investigational sites, study period, patient selection criteria, and success/failure criteria) and include the data collection and reporting procedures that will be used to determine whether the device is safe and effective for its intended use. It is also important that the study be designed and conducted in a manner that provides data which will constitute valid scientific evidence within the meaning of 21 CFR 860.7. The investigation is a clinical trial, not a compilation of available patient records. Proper monitoring of the study, accountability for all patients, and documentation and evaluation of reasons for patient discontinuation are essential.

The following is a discussion of the major elements of a typical clinical study and suggested methodologies to be included in the protocol. [Appendices 4 through 12](#) of the clinical section of the document include sample visitation observation forms and patient complication forms. Situations and issues to be addressed will vary with different device types and intended uses; the clinical investigations must be tailored to meet specific needs. When questions remain concerning the protocol or content and form of an IDE each sponsor should consult with DGRD prior to finalizing their clinical protocol and initiating the investigation.

OVERVIEW OF CRITICAL CLINICAL TRIAL ELEMENTS

CDRH requires PMA data on statistically justified number of study patients receiving an investigational device (device patients) in a prospective multicenter clinical study with 2-year follow-up for each injury class (e.g., 50 chronic ACL patients with 2-year follow-up, etc.). Injury classes are defined below. These are the minimum data necessary to evaluate device safety and effectiveness. Longer follow-up (up to 5 years) may be required. The rationale for the number of patients in each category must take into account the pooling of data from multiple investigators, with an adequate number of patients per investigator, as discussed below, and also to allow the detection of low incident complications. It is necessary for the sponsor to provide a statistical justification for the number of study patients requested based on the ability to detect differences between the device patients and control group with a given power, the expected failure/explant rate, and the expected lost to follow-up rate. FDA in the past has used 100 device patients and 100 control patients as a rule of thumb but the statistical calculations could justify a request for significantly more than 100 device patients or less.

The sponsor must provide PMA data on prospective concurrent control patients who have received accepted medical treatment. This control group should consist of patients with autogenous reconstructions performed by surgeons experienced in these techniques. Randomization of patients into the control and device groups is strongly encouraged. CDRH is recommending a 1:1 entry of control and device patients into the study. Each investigator must have control and device patients. Furthermore, follow-up by evaluators not knowing the treatment status can provide a more objective evaluation of the patients. Using the patient as his/her own control presents many problems. The exclusive use of historical and/or retrospective comparative data is not acceptable. However, CDRH recognizes that problems may arise in providing a control group for certain patients, i.e., "salvage" patients (defined below).

It is advisable to subdivide a clinical study into two phases. A two phase study is beneficial for significant risk devices of new materials or new intended uses. Phase I should be a single center pilot or feasibility study. A pilot study can help identify device related problems and user related problems with risk to a minimum number of patients. Phase II should be the multicenter clinical trial.

In the prospective multicenter clinical trial of ACL repairs, CDRH recommends at least 6 surgeons/investigators with a minimum of 10 to 15 device implant procedures per surgeon. Too few patients per investigator per treatment category will decrease the probability of a given investigator having representative patients of a given injury type, and will make difficult the analysis of failure rate versus experience gained. However, concentration of patients with a single investigator or at a single investigational site should be avoided. The Orthopedic and Rehabilitation Devices Advisory Panel has recommended that each investigator's relationship to the sponsor (e.g., paid clinical consultant, company owner, etc.) be disclosed.

DGRD has defined an acute injury as one which has occurred less than or equal to 3 weeks prior to surgery. A subchronic injury is one which has occurred more than 3 weeks and up to 6 months prior to surgery. Lastly, a chronic injury is defined as one which has occurred more than 6 months prior to surgery. "Salvage" ACL patients are defined as patients having a previous failed intra-articular autogenous ACL reconstruction. CDRH recommends that any ACL device clinical trial should contain a chronic cohort.

PCL injuries are much less common than ACL injuries. Difficulties may arise in obtaining 10 to 15 patients per investigator per treatment category within a reasonable time frame and also in obtaining 100 patients in both the device and control groups. These problems will be considered by CDRH when reviewing IDE and PMA applications for PCL repairs.

SUGGESTED CLINICAL PROTOCOLS

Patient Characteristics

Patients entered in the clinical trial should have the following characteristics.

1. There must be a well documented ligament deficiency by history and physical examination. The actual appearance of the ligament should be documented at the time of

surgery. If combined ligamentous injuries are present, the sponsor must justify pooling the data.

2. Patients must be old enough to give informed consent.
3. Both tibial and femoral epiphyses must be closed.
4. There are no upper age limitations; however, it is anticipated that patients over 45 will be rare and the median patient age will be 25 to 30 years for chronic ACL first time reconstructions.

The following patients should be excluded from the study:

1. patients with active articular infections;
2. patients with metabolic bone disease, e.g., osteoporosis, rickets;
3. patients with crystal deposition disease, e.g., gout;
4. patients with inflammatory joint disease, e.g., rheumatoid arthritis;
5. patients with severe degenerative joint disease (CDRH recognizes that many chronic patients will have minimal osteoarthritic changes, which should be well documented by the sponsor);
6. patients with known neoplastic disease;
7. patients with a medical condition that interferes with their ability to participate in a rehabilitation program; and
8. patients who the physician thinks are unlikely to comply with, or participate in, the rehabilitation program and return for follow-up visits. Geographic location should be a consideration.

In addition, DGRD believes that patients with local circulatory problems such as thrombophlebitis and lymphedema may be at higher risk for complications. Furthermore, the inclusion of patients with contralateral knee pathology, particularly ligamentous instability, may present problems both for side-by-side comparisons (e.g., Lachman score) and also for pooling patients' data (e.g., the rehabilitation may be more difficult for the patient with bilateral knee pathology).

Initial Evaluation

An initial visit examination form (in the form of [Appendix 4, 5, and 6](#)) should be filled out and signed at the time of the initial visit by the investigator or co-investigator performing the examination. Please note that the ACL evaluation format presented in [Clinical Orthopedics and Related Research](#) 218: 167, 1987, Lukianov, et al, is an acceptable alternative. If the sponsor wishes to use a different scale for the pivot shift than that shown in [Appendix 6](#) (e.g., a 0 to 3

scale instead of a 0 to 4), the chosen scale should be fully explained. Patients should be informed that up to 5 years of follow-up may be required. In addition to routine clinical chemistry, the sponsor may find it useful to freeze preoperative sera to help evaluate later unexpected clinical findings.

Operative Evaluation

The operative evaluation form ([Appendix 7](#)) and physical examination form ([Appendix 6](#)) should be completed.

Follow-Up Evaluation

All patients (both in the device and control groups) should be on the same follow-up visit schedule. The schedule for patient evaluation should be as follows: preoperative, intraoperative (pre-repair), 3, 6, 12, 18, and 24 months. Data collected for patients at greater than 2 years post-implantation should be presented at 12-month increments.

For each of these visits a follow-up examination form (in the form of [Appendix 5](#) and [Appendix 6](#)) is to be filled out and signed by the investigator or co-investigator performing the examination. However, the laxity testing portion of [Appendix 6](#) is optional at the 3-month follow-up. In addition, arthrometer testing to measure laxity at 20° of flexion and isokinetic testing is recommended.

A comparison of the rehabilitation, including the milestones of rehabilitation, between the study and control groups is one of the most important aspects of the study. This comparison of rehabilitation must include a detailed time course for the following: immobilization, protection (e.g., partial weight bearing), type of exercise, and activity.

Other Medical Data

The IDE and PMA should contain a detailed operative illustration. Also, a description of the revision procedure in the event of device explantation should be provided. A demonstration "model" knee with the device in place should be provided to CDRH.

CDRH recommends that a uniform study protocol be used for post-implantation antibiotic prophylaxis for patients undergoing dental work, instrumentation, etc. If antibiotic prophylaxis will be used in the study, this information must be included in the informed consent. Any special operative room measures to improve sterility should be discussed. The study protocol of any clinical immunological evaluations (antibody titers, sensitivity testing) should be provided in the IDE.

PRESENTATION OF CLINICAL DATA

Safety Data

Presentation of data for the device group should include, but not be limited to, the following complication and failure analysis information. These data must be submitted in IDE progress and annual reports as well as in the PMA. In the PMA, data from original study device

implantations must be presented and analyzed separately from subsequent device implantations at the same anatomic site (e.g., if the first study device falls and is replaced with a second device). Also, data from foreign investigation sites must be presented and analyzed separately from U.S. data. In addition to the separate presentation of the U.S. and foreign data, the sponsor may pool such data with justification.

If any of the following are observed, the occurrence must be fully documented and should be reported as shown in [Appendix 8](#). This is a patient by patient listing of complication details.

1. any evidence (clinical or physical exam) that the device has ruptured; data on device rupture to include detailed pathological evaluation of all explanted devices and any diagnostic pathology relevant to a complication;
2. the occurrence of a poor clinical outcome, including instability/laxity;
3. joint swelling or tenderness that is persistent beyond the initial postoperative period; data on joint effusions to include volume and appearance of fluid, cell count with differential, examination for particulate matter, and any other relevant data;
4. joint infection or systemic infection; data on infections to include culture results; and
5. synovitis (if a biopsy is performed, diagnostic pathology reports must be submitted).

Any other complications, or significant intercurrent medical events, device related or otherwise, must also be reported in the IDE progress and annual reports as well as in the PMA.

To facilitate failure analysis, the patients with the following results should be identified (list the study number) in the PMA clinical summary (whether or not the event is considered to be device-related). This should be done for both the entire population and also the 2-year (or longer) follow-up cohort.

1. explantation for any reason, including infection; providing the reason for explantation (for example, 10 explants for device rupture, 5 explants for infection, etc.);
2. device rupture, whether or not related to trauma;
3. any resurgery of the reconstruction, including retensioning;
4. any other resurgery of the knee, including total knee replacement and amputation;
5. cases of synovitis and effusion;
6. cases of local infection and any serious systemic infection; separately, identify patients with intra-articular infections;
7. cases of laxity; all patients with a Lachman of $\geq 2+$;

8. a regression of successive laxity scores (taken under the same conditions) over at least 1 year with no improvement by the final examination, for any score;
9. no improvement of ≥ 2 grades on the Lachman scores, for ACL patients;
10. cases of instability; all patients experiencing giving way with activities of daily living, it may be useful to identify other subsets of patients (giving way with sports, etc.);
11. any pain with activities of daily living that is no better at the latest examination than pre-operatively/post-injury; and
12. no improvement in function at the latest examination compared to pre-operatively/post-injury.

In addition, the number of patients in each of the above categories should be tabulated (e.g., 10 device ruptures, 12 cases of synovitis, etc.) and patients in more than one category should be identified. This tabulation should be performed for both the entire group and also the 2-year (or longer) follow-up cohort. For each complication (e.g., device rupture) or event (e.g., device explant), the number of complications/ events should be plotted as a function of time post-implantation of initial occurrence, using 1- or 2-month increments. At a minimum, such graphs (see [Appendix 11 B](#)) should be prepared for each of the following complications/events: device rupture, device explant, synovitis/effusion, intra-articular infections, and instability with activities of daily living. The number of patients having explants, device ruptures, and cases of instability for both the entire populations and the 2-year (or longer) follow-up cohort, should also be tabulated. The sponsor may find it useful to tabulate the number of patients in various combinations of items (1) through (12) of the failure analysis data. Please note that patients with complications will not necessarily be considered failures. For items such as synovitis, the severity of the problem will be considered.

A summary and analysis of complications and significant intercurrent medical events not mentioned in failure analysis data (1) through (12) above, should include the incidence of each type of complication/event for both the entire study population and the 2-year (or longer) cohort. In some instances, complications/events will be considered failures.

Effectiveness Data

Presentation of PMA data for both the autogenous control and also the device group should include, but not be limited to, the following effectiveness information. Data from original study device implantations must be presented and analyzed separately from subsequent device implantations at the same anatomical site (e.g., if the first study device fails and is replaced with a second device) for items 1 through 10 below.

1. The PMA should clearly state the number of patients eligible for the cohort at the time point used for final evaluation. In the PMA, the term "cohort" should refer to the post-implantation group. For example, if the sponsor presents data and statistical analysis on 150 device patients at 2 years, but an additional 15 patients who are 2 years post-implantation were lost to follow-up and an additional 6 patients who were 2 years post-implantation had the device explanted before 2 years due to complications, the document

should state that a total of 171 device patients were in the ~2-year cohort (2 years or more post-implantation). The sponsor must continue to follow device patients whose device has been explanted.

A summary patient accountability table as shown in [Appendix 12](#) should be completed.

2. A list and an analysis of the lost to follow-up patients, including the information requested in [Appendix 9](#) should be provided.
3. Pooling data from different investigators and different centers must be justified. This justification should include an investigator by investigator listing of a) the incidence of each complication and also incidence of other problems associated with a poor clinical outcome, such as laxity/instability and b) the number of patients lost to follow-up. These data can be compared to the overall incidence for each item. Also, there should be a list of investigators with the number of patients per investigator.
4. Pooling data from patients with different characteristics such as different activity levels (e.g., sedentary versus competitive athlete), different degrees of initial knee pathology (e.g., radiographic degenerative changes versus no radiographic changes), and different previous surgeries (e.g., previous ACL reconstruction versus no previous knee surgery) must be justified.
5. Distribution of scores for each objective item from [Appendix 6](#) and subjective assessment from [Appendix 5](#) for the entire population, at each time point of data collection, for all device patients in a group (e.g., study device group) should be presented according to [Appendix 11](#).
6. Distribution of scores for each evaluation item for only the 2-year or more cohort (or other cohort) at each time point of data collection, for patients in a given group should be presented according to [Appendix 11](#).
7. A patient by patient listing of the Lachman and pivot shift laxity scores in a separate table, for the ACL patients should be presented according to [Appendix 11 A](#).
8. Follow-up arthroscopic and surgical data must be included and should include a description of the condition/appearance of the device and intra-articular structures, with a comparison to that seen at initial implantation.
9. Stratification of success/failure versus patient characteristics should be provided.
10. Analysis and statistical tests of significance should be provided (see "Guidance for Clinical Investigations for a PMA" in the Premarket Approval (PMA) Manual). This should include a statistical comparison of the study patients with the control patients for all evaluation items, including rehabilitation, and complications. A life table projection of device failures at 5 and 10 years, with details of the calculation, should also be provided. For these life table analyses, device failures can include device breakage, and instability/laxity, and explantation for any reason. Statistical evidence of the device's effectiveness is essential for PMA approval.
11. A separate volume(s), with the patient by patient data, as suggested in [Appendix 10](#) must be included. This does not substitute for a presentation and discussion of complications in the clinical summary.

APPENDIX 1

TENSILE TEST DATA

	Strain Rate (%/sec)	Yield Load (N)	Yield Elongation (%)	Failure or Ultimate Load (N)	Failure or Ultimate Elongation (%)	Stiffness (N/mm)
--	------------------------	-------------------	-------------------------	---------------------------------	---------------------------------------	---------------------

Preconditioned Device

Device Soaked For 1 Month In 37°C Saline

	Strain Rate (%/sec)	Yield Stress (MPa)	Yield Strain (%)	Failure or Ultimate Stress (MPa)	Failure or Ultimate Strain (%)	Modulus (N/m ²)
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Preconditioned Device

Device Soaked For 1 Month In 37°C Saline

APPENDIX 2

TENSILE FATIGUE TEST DATA

Cycle Rate (Hz)	Peak Load (N)	Number of Cycles	Total Elongation* (%)	Failure Load (N)	Failure Elongation* (%)	Stiffness (N/mm)
Device						

*Permanent elongation at zero load; relaxed length.

Note: Failure Load, Failure Elongation, and Stiffness are to be determined in tensile tests if failure does not occur by 1×10^7 cycles.

APPENDIX 3

BEND FATIGUE TEST DATA

Cycle Rate (Hz)	Peak Axial Load (N)	Angle of Bending	Number of Cycles	Total Elongation* (%)	Failure Load (N)	Failure Elongation* (%)	Stiffness N/mm)
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Device

*Permanent elongation at zero load; relaxed length.

Note: Failure Load, Failure Elongation, and Stiffness are to be determined in tensile tests if failure does not occur by the predetermined design life.

APPENDIX 4

STUDY ENROLLMENT / ELIGIBILITY / PATIENT HISTORY

Patient Name: _____ Study #: _____
Sex: _____
Address: _____
Telephone Number: _____
Birthday: _____

Name Of Closest Friend/Relative Not Living With Patient: _____
Address: _____
Telephone Number: _____

Investigation Site: _____
Physician: _____
Patient Classification: _____
Date Of Original Knee Injury: _____
Date Of Entry Into Study: _____
Patient Age At Injury: _____

Patient Eligible for Study Based on Criteria Below: YES NO
Note: a "YES" answer to any questions below means that the patient is not eligible for the study.

HISTORY OF: YES NO

Metabolic Bone Disease (e.g., Osteoporosis, Rickets)

Joint Infection Or Systemic Infection

Crystal Deposition Disease (E.G., Gout)

Inflammatory Joint Disease (E.G., Rheumatoid Arthritis)

Periarticular or Patella Fracture

Known Neoplastic Disease

Epiphyses That Have Not Yet Closed

Medical Condition That Interferes With Ability To Participate In A Rehabilitation Program

Other Reason (Please Specify) That Patient Is Unlikely To Participate In Rehabilitation Or Return For Follow-Up Visits

Cause Of Injury (Athletic, Traffic Accident, Etc.): Name Sport If Applicable

Symptoms At Injury (Yes or No Response):

Pop _____ Pain _____ Swelling _____

If Sports Related, Able To Continue Activity Immediately After Injury _____

Time After Injury Before Evaluation By Physician: _____

Previous Diagnostic Arthroscopy: Yes _____ No _____

Findings and Date: _____

PREVIOUS TREATMENT:

	<u>YES</u>	<u>NO</u>	<u>If YES, Give Date(s)</u>
Surgery			
Primary ACL Repair			
Intra-Articular ACL Reconstruction			
Previous Prosthetic ACL Ligament			
Extra-Articular Reconstruction			
MCL Repair			
MCL Reconstruction			
LCL Repair			
LCL Reconstruction			
PCL Reconstruction			
Meniscus Surgery			
Conservative			
Complication, if any			

Details of any previous treatment to include exact type of previous surgery (e.g., partial medial meniscectomy) and description of autogenous or allograft tissue used (e.g., autogenous patellar tendon ACL reconstruction). If applicable, complications, etc.

Tegner Activity Level (See Appendix 5A) Prior To Injury:

Radiographic Findings (Degenerative Changes, etc.):

Comments:

Date:

Investigator Completing Report (Print):

Investigator Completing Report (Signature):

APPENDIX 5

PRE AND POSTOPERATIVE SYMPTOMS AND FUNCTION LEVEL

Patient Name:

Study Number:

PAIN:

LEFT RIGHT

No Pain, Normal Knee, Performs 100%

Occasional Pain With Strenuous Sports Or Heavy Work, Knee Not Entirely Normal,
Some Limitation But Minor And Livable

Occasional Pain With Light Recreational Sports Or Moderate Work Activities,
Frequently Brought On By Vigorous Activities, Running, Heavy Labor, Strenuous
Sports

Pain, Usually Brought On By Sports, Light Recreational Activities Or Moderate Work.
Occasionally Occurs With Walking, Standing Or Light Work.

Pain Is A Significant Problem With Activities As Simple As Walking. Relieved By Rest.
Unable To Do Sports.

Pain Present All The Time, Occurs With Walking, Standing And At Night-Time. Not
Relieved With Rest.

Not Known. I Have Not Tested My Knee.

Intensity of Pain:

Right: Mild Moderate Severe

Left: Mild Moderate Severe

Location of Pain:

Right: Medial Lateral Anterior-Patellar Posterior Diffuse

Left: Medial Lateral Anterior-Patellar Posterior Diffuse

Pain Occurs On:

Right: Stairs Sitting Kneeling Standing

Left: Stairs Sitting Kneeling Standing

Type Of Pain:

Right: Sharp Aching Throbbing Burning

Left: Sharp Aching Throbbing Burning

GIVING WAY:

RIGHT LEFT

No Giving Way, Normal Knee, Performs 100%

Occasional Giving Way With Strenuous Sports Or Heavy Work. Can Participate In All
Sports But Some Guarding Or Limitations Are Still Present.

Occasional Giving Way With Light Recreational Activities Or Moderate Work. Able To
Compensate, Limits Vigorous Activities, Sports Or Heavy Work; Not Able To
Cut Or Twist Suddenly.

Giving Way Limits Sports And Moderate Work, Occurs Infrequently With Walking Or
Light Work (About 3 Times/Year)

Giving Way With Simple Walking Activities And Light Work. Occurs Once Per Month.
Requires Guarding.

Severe Problem With Simple Walking Activities Cannot Turn Or Twist Without Giving Way
Not Known. I Have Not Tested My Knee.

SWELLING:

RIGHT LEFT

No Swelling, Normal Knee, 100% Activity
Occasional Swelling With Strenuous Sports Or Heavy Work. Some Limitations But Minor And Liveable.
Occasional Swelling With Light Recreational Sports Or Moderate Work Activities, Frequently Brought On By Vigorous Activities, Running, Heavy Labor, Strenuous Sports
Swelling Limits Sports And Moderate Work. Occurs Infrequently With Simple Walking Activities Or Light Work (About 3 Times Per Year)
Swelling Brought On By Simple Walking Activities And Light Work. Relieved With Rest.
Severe Problem All Of The Time, With Simple Walking Activities
Not Known. I Have Not Tested My Knee.

Intensity:

Right:	Mild	Moderate	Severe
Left:	Mild	Moderate	Severe

Frequency:

Right:	Intermittent	Constant
Left:	Intermittent	Constant

STIFFNESS:

RIGHT LEFT

No Stiffness, Normal Knee, 100% Activity
Occasional Stiffness With Strenuous Sports Or Heavy Work.
Occasional Stiffness With Light Recreational Sports Or Moderate Work Activities. Frequently Brought On By Vigorous Activities.
Stiffness Limits Sports And Moderate Work. Occurs Infrequently With Simple Walking Activities Or Light Work
Stiffness Brought On By Simple Walking Activities And Light Work. Relieved With Rest.
Severe Problem All Of The Time, With Simple Walking Activities
Not Known. Knee Not Tested.

FUNCTIONAL ACTIVITY
RIGHT LEFT

No Limitation, Normal Knee, Able To Do Everything Including Strenuous Sports Or Heavy Labor If Desired.

Perform Sports Including Vigorous Activities, But At A Lower Performance Level, Involves Guarding Or Some Limits To Heavy Labor Activity

Light Recreational Activities Possible With Rare Symptoms, More Strenuous Activities Cause Problems. Active But In Different Sports, Limited To Moderate Work.

No Sports Or Recreational Activities Possible. Walking Activities Possible With Rare Symptoms, Limited To Light Work.

Walking, Activities Of Daily Living Cause Moderate Symptoms, Frequent Limitation

Walking, Activities Of Daily Living Cause Severe Problems, Persistent Symptoms

Not Known. I Have Not Tested My Knee Or I Have Given Up Strenuous Sports.

FUNCTIONS (5 items)

RIGHT LEFT

Walking

Normal, Unlimited

Slight, Mild Problem

Moderate Problem: Smooth Surface OK Up To 1/2 Mile

Severe Problem: Only 2-3 Blocks Possible

Severe Problem: Requires Cane, Crutches

Climbing Stairs

Normal, Unlimited

Slight, Mild Problem

Moderate Problem: Only 10 To 15 Steps Possible

Severe Problem: Requires Banister, Support

Severe Problem: Only 1-5 Steps Possible

Descending Stairs

Normal, Unlimited

Slight, Mild Problem

Moderate Problem: Only 10 To 15 Steps Possible

Severe Problem: Requires Banister, Support

Severe Problem: Only 1-5 Steps Possible

Running Activity

Normal, Unlimited Fully Competitive, Strenuous

Slight, Mild Problem: Run Half Speed

Moderate Problem: Only 1-2 Miles Possible

Severe Problem: Only 1-2 Blocks Possible

Severe Problem: Only A Few Steps

Jumping Or Twisting Activities

Normal, Unlimited, Fully Competitive, Strenuous

Slight, Mild Problem: Some Guarding, But Sports OK

Moderate Problem: Gave Up Strenuous Sports But Recreational Sports OK

Severe Problem: Affects All Sports, Must Constantly Guard

Severe Problem: Only Light Activity Possible (Golf, Swimming)

Modified from:

Noyes, Frank R., McGinniss, George H., and Grood, Edward S. The Variable Functional Disability of the Anterior Cruciate Ligament-Deficient knee. The Orthopedic Clinics of North America. 16: 60, 1985

SUPPORT/ACTIVITIES OF DAILY LIVING

Knee Brace: Yes _____ No _____ Type _____

Cane: Yes _____ No _____

Other Support: Yes _____ No _____,

Comment _____

SUPPORT/ATHLETICS

Knee Brace: Yes _____ No _____ Type _____

Cane: Yes _____ No _____

Other Support: Yes _____ No _____,

Comment _____

APPENDIX 5A

TEGNER ACTIVITY LEVEL SCALE

- Level 10. Competitive sports - soccer, football, rugby (national elite)
- Level 9. Competitive sports - soccer, football, rugby (lower divisions); ice-hockey, wrestling, gymnastics, basketball
- Level 8. Competitive sports - racquetball or bandy, squash or badminton, track and field athletics (jumping, etc.), Down-hill skiing
- Level 7. Competitive sports - tennis, running, motorcross speedway, handball
Recreational sports - soccer, football, rugby, bandy and ice-hockey, basketball, squash, racquetball, running
- Level 6. Recreational sports - tennis and badminton, handball, racquetball, down-hill skiing, jogging at least 5 times per week
- Level 5. Work - heavy labor (construction, etc.)
Competitive sports - cycling, cross-country skiing
Recreational sports - jogging on uneven ground at least twice weekly
- Level 4. Work - moderately heavy labor (e.g. Truck driving, etc.)
Recreational sports - cycling, cross-country skiing, jogging on even ground at least twice weekly.
- Level 3. Work - light labor (nursing, etc.)
Backpacking or hiking, swimming
- Level 2. Work - light labor
Walking on uneven ground possible but impossible to backpack or hike
- Level 1. Work - sedentary (secretarial, etc.)
Walking on even ground possible
- Level 0. Sick-leave or disability pension because of knee problems

Y. Tegner and J. Lysolm. Rating Systems. in the Evaluation of Knee Ligament Injuries. Clinical Orthopedics and Related Research. Vol. 198: 43-49, 1985.

APPENDIX 6

PRE AND POSTOPERATIVE PHYSICAL EXAM

Patient Name: _____ Study #: _____
Patient Status: _____
Height: _____
Weight: _____

Lachman (20° Flexion): 0, +1, +2, +3, +4 (RIGHT)
 0, +1, +2, +3, +4 (LEFT)
 side to side difference in mm _____

Anterior Drawer, Neutral Rotation (90° Flexion):
 0, +1, +2, +3, +4 (RIGHT)
 0, +1, +2, +3, +4 (LEFT)
 side to side difference in mm _____

*Pivot Shift: 0, +1, +2, +3, +4 (RIGHT)
 0, +1, +2, +3, +4 (LEFT)

Valgus Laxity At 25° Flexion: 0, +1, +2, +3, +4 (RIGHT)
 0, +1, +2, +3, +4 (LEFT)

Valgus Laxity At 0° Flexion: 0, +1, +2, +3, +4 (RIGHT)
 0, +1, +2, +3, +4 (LEFT)

Varus Laxity At 25° Flexion: 0, +1, +2, +3, +4 (RIGHT)
 0, +1, +2, +3, +4 (LEFT)

Varus Laxity At 0° Flexion: 0, +1, +2, +3, +4 (RIGHT)
 0, +1, +2, +3, +4 (LEFT)

Posterior Drawer (90° Flexion): 0, +1, +2, +3, +4 (RIGHT)
 0, +1, +2, +3, +4 (LEFT)
 side to side difference in mm _____

Posterior Sag (90° Flexion): 0, +1, +2, +3, +4 (RIGHT)
 0, +1, +2, +3, +4 (LEFT)

Thigh Circumference: 5cm Above Patella Right _____ Left _____
 15cm Above Patella Right _____ Left _____

Valgus And Varus Alignment (Clinical, X-Ray, Etc.): _____

Range Of Motion: From _____° to _____°

Patellofemoral Joint:

Patellofemoral Crepitus:

Patellofemoral Pain:

Relative Height Of Patella:

Apprehension To Lateralward Pressure:

Radiographic Evaluation Of Patellofemoral Joint:

Effusion Present (0-3): None ____ Mild ____ Moderate ____ Severe ____

Lab Results (WBC With Differential On Aspirated Fluid, Etc.): ____

Comment: _____

Meniscus Test (Could Include: Palpation Of Both Menisci At Joint Line To Locate Tenderness, Detection Of Catch Or Pop, McMurray Test):

Neurovascular, Status (To Include Palpation Of Popliteal, Posterior Tibial, And Dorsalis Pedis Pulses):

LAXITY GRADING SYSTEM:

- 0 No Excess Laxity
- +1 Up To 5mm Excess Laxity
- +2 6 To 10mm Excess Laxity
- +3 11 To 15mm Excess Laxity
- +4 Greater Than 15mm Excess Laxity

***PIVOT SHIFT GRADING SYSTEM:**

- 0 Negative
- +1 (Mild) Flexion-Rotation Drawer +1, Can Be Physiologic Laxity
- +2 (Moderate) Subtle Subluxation. Reduction That Is Detected As A "Slide" Or "Slip" Rather Than An Obvious "Jump", "Thud" Or "Jerk"
- +3 (Severe) Gross Subluxation. Reduction With Obvious "Jump", "Thud", Or "Jerk"
- +4 (Gross) Gross Impingement Of The Lateral Femoral Condyle In Front Of The Tibia During Subluxation, Requiring "Backing Off" To Achieve Reduction

*F.R. Noyes, E.S. Grood, W.J. Suntay, and D.L. Butler. The Three Dimensional Laxity Of The Anterior Cruciate Deficient Knee As Determined By Clinical Laxity Tests. The Iowa Orthopedic Journal Vol. 3: 32-44, 1983.

*B. Zarins and C.R. Rowe. Combined Anterior Cruciate-Ligament Reconstruction Using Semitendinosus Tendon And Iliotibial Tract. The Journal Of Bone And Joint Surgery. Vol. 68-A: 160-177, 1986

Date:

Physician (Printed):

Physician (Signature):

APPENDIX 7

OPERATIVE FORM

Patient Name:

Patient Study Number:

Patient Classification (Acute ACL, Chronic ACL, Control PCL, etc.):

Investigational Site:

Date of Surgery:

Operative Chronology For This Physician (1st Implant, etc.):

Preoperative Diagnoses:

Presurgical Examination Under Anesthesia - Use Appendix 6.

Complete Description Of All Intra-Articular Structures:

Surgery Performed, Including Exact Description Of Autogenous Tissue Used.

Intraoperative Complications:

Postoperative Diagnosis:

Tournique Time:

Antibiotics, Intraoperatively (State if Topical, IV, etc.):

Antibiotics, Postoperatively:

Implant Serial Number:

Date:

Surgeon's Name (Printed):

Surgeon's Name (Signature):

APPENDIX 8

REPORT OF DEVICE FAILURES / RUPTURES OR “CLINICAL FAILURES”

1. Patient Study Number
2. Investigator
3. Investigation Site
4. Surgical Procedure
5. Diagnosis With Initial Classification (Chronic Injury, etc.)
6. Time Interval In Months From Implant Surgery To Onset Of Complication, Including Actual Dates (e.g., 12 Months, 1/12/86-1/87).
7. Type Of Complication.
8. Pertinent Laboratory Data (Microbiology Results, etc.).
9. If Complication Was Activity/Sport Related State What Activity/Sport.
10. Treatment Of Complication.
11. Time From Original Surgery That Second Device Was Implanted, If Applicable.
12. Latest Status Of Patient (Should State Time Post-Implantation And Should Include Evaluation Of Pain, Limitation Of Range Of Motion, Function, And Stability).
13. State If Complication Is Device Related. Give Justification.
14. State Site Where Device Ruptured (At Entrance To Tibial Tunnel, etc.), If Applicable.
15. Additional Information.
16. Attached Pathology Report, If Available, And Commentary.

APPENDIX 9

PATIENT LOST TO FOLLOW-UP

Patient Name:

Study Number:

Patient Age:

Investigator:

Classification Of Injury (E.G., Chronic ACL, etc.):

Date Of Implantation:

Time Post-Implantation Of Recorded Follow-Ups, Including Time Post-Implantation Of The Last Follow-Up:

Clinical Status At Last Follow-Up (Include Stability Assessment, Range Of Motion, Complications):

Time Post-Implantation Of Follow-Up Visit That Was Due And Missed:

Reason For Lost To Follow-Up And Documentation:

APPENDIX 10

**SUGGESTED TABULAR PRESENTATION OF THE
INDIVIDUAL PATIENT STUDY DATA**

Patient I.D.:

Investigator:

Date Of Implantation:

Patient Classification (Chronic ACL, etc.):

Complications:

EVALUATION ITEM

	<u>Pre-Op</u>	<u>Post-Op</u>	<u>3mo</u>	<u>6mo</u>	<u>12mo</u>	<u>18mo</u>	<u>24mo</u>	<u>36mo</u>
Lachman								
Pivot Shift								
Anterior Drawer, 90° Flexion								
Posterior Drawer, 90° Flexion								
Valgus Laxity, 0° Flexion								
Valgus Laxity, 25° Flexion								
Varus Laxity, 0° Flexion								
Varus Laxity, 25° Flexion								
Posterior Sag, 90° Flexion								
Range Of Motion								
Giving Way								
Pain								
Joint Effusion								
Extra-Articular Swelling								
Etc.								

APPENDIX 11

**PRESENTATION OF INDIVIDUAL EVALUATION ITEMS
FOR THE PATIENT POPULATION**

Item	Time Point							
	<u>Pre-Op</u>	<u>Post-Op</u>	<u>3mo</u>	<u>6mo</u>	<u>12mo</u>	<u>18mo</u>	<u>24mo</u>	<u>36mo</u>
LACHMAN SCORE								
0								
+1								
+2								
+3								
+4								
Total #Patients At Each Time								

APPENDIX 11 A

**PRESENTATION OF PATIENT BY PATIENT
LAXITY SCORES IN THE CLINICAL SUMMARY**

Item: Lachman Score

Time Point

PATIENT IDENTIFICATION

Pre-Op

Post-Op

3mo

6mo

12mo

18mo

24mo

36mo

Patient #11

Patient #2

Patient #3

Etc.

Designate Patients Lost To Follow-Up.

APPENDIX 11 B

NUMBER OF PATIENTS AS A FUNCTION OF TIME OF COMPLICATION/EVENT*

Complication: Device Ruptures, 2 Yr Cohort

Total Number: N

of Patients

etc. |

5 |

4 |

3 |

2 |

1 |

0 2 4 6 8 10 12 14 16 18 20 22 24 26, etc.

Months Post-Implant, Time That Complication First Occurred

* May Be Presented As A Bar Graph

APPENDIX 12

PATIENT ACCOUNTABILITY TABLE

Patients In A Given Class Of Injury (Chronic ACL Patients With First Implant Of Study Device, Etc.)

1. *Patients 2 Years Or More Post-Implant
 - 1a. _____ Patients With 2 Yrs Follow-Up Available, Device In Place
 - 1b. _____ Patients With 2 Yrs Follow-Up Available, Device Explanted
 - 1c. _____ Patients Lost To Follow-Up Prior To 2 Yrs, Device In Place At Last Follow-Up
 - 1d. _____ Patients Lost To Follow-Up Prior To 2 Yrs, Device Explanted By Last Follow-Up

2. Patients Less Than 2 Years Post-Implant
 - 2a. _____ Patients Still Being Followed, Device In Place
 - 2b. _____ Patients Still Being Followed, Device Explanted
 - 2c. _____ Patients Lost To Follow-Up, Device In Place At Last Follow-Up
 - 2d. _____ Patients Lost To Follow-Up, Device Explanted By Last Follow-Up

*Sponsor may also use a longer than 2-year cohort.

In the example given above, the sum of patients 1a through 1d must equal the number of 2 year cohort patients (1 above) and the sum of patient 2a through 2d must equal the number of patients less than 2 years post-implant (2 above).

REFERENCES

Ames, B.N., McCann, J., and E. Yamasaki, Methods for Detecting Carcinogens and Mutagens with the Salmonella/Mammalian-Microsome Mutagenicity Test, Handbook of Mutagenicity Test Procedures, Kilbey, Legator, Nichols, and Ramel (Ed), Elsevier Scientific Publishing Co., Amsterdam, pp. 1-18, 1977.

J. Autian, Toxicological Evaluation of Biomaterials. Primary Acute Toxicity Screening Programme, Artificial Organs, 1: 53-60, 1977.

Biological Tests - Plastics, United States Pharmacopeia, 20th Edition, p. 950, Rockville, MD (1980).

Chen, E.H., and J. Black, Material Design Analysis of the Prosthetic Anterior Cruciate Ligament, Journal of Biomedical Materials Research, 14: 567-586, 1980.

Clive, D., and J.F.S. Spector, Laboratory Procedure for Assessing Specific Locus Mutations at the TK Locus in Cultures of L5178Y Mouse Lymphoma Cells, Mutation Research, 31: 17-29, 1975.

Dermal and Eye Toxicity Tests, Principles and Procedures for Evaluating the Toxicity of Household Substances, National Academy of Science, Washington D.C., pp. 23-59, 1977

Grood, E., and F. Noyes, Cruciate Ligament Prosthesis: Strength, Creep, and Fatigue Properties, Journal of Bone and Joint Surgery, 58A: No 8, 1083-1088, 1976.

Heidelberger, C., et al., Cell Transformation by Chemical Agents - A Review and Analysis of the Literature. A Report of the U.S. Environmental Protection Agency Gene-Tox Program, Mutation Research, 114: 283-385, 1983.

Hsie, A.W., Couch, D.B., O'Neill, J.P., et al., Utilization of a Quantitative Mammalian Cell Mutation System, CHO/HGPRT, in Experimental Mutagenesis and Genetic Toxicology. Strategies for Short-Term Testing for Mutagens/Carcinogens. Butterworth, B.E. (Ed), CRC Press, West Palm Beach Florida, pp. 39-54, 1979.

M.W. King, R. Guidoin, P. Blais, A. Garton, and K.R. Gunasekera. Degradation of Polyester Arterial Prosthesis: A Physical or Chemical Mechanism? Special Technical Testing Publication 859. Copyright American Society for Testing and Materials. 1916 Race Street, Philadelphia, PA 19103, pp.294-307, 1985.

J.C. Kennedy, R.J. Hawkins, R.B. Willis and K.D. Danylchuk. Tension Studies of Human Knee Ligaments. The Journal of Bone and Joint Surgery, Vol. 58-A, pp.350-355, 1976.

A.V. Lukianov, J. Gillquist, W.A. Grana, K.E. DeHaven. An Anterior Cruciate Ligament (ACL) Evaluation Format for Assessment of Artificial or Autologous Anterior Cruciate Reconstruction Results. Clinical Orthopedics and Related Research, 218: 167-180, 1987.

Mitchell, A.D., et al., Unscheduled DNA Synthesis Tests. A Report of the U.S. Environmental Protection Agency Gene-Tox Program, Mutation Research, 123: 363-410, 1983.

F.R. Noyes and E.S. Grood. The Strength of the Anterior Cruciate Ligament in Humans and Rhesus Monkeys. The Journal of Bone and Joint Surgery, Vol. 58-A: 1074-1082, 1976.

F.R. Noyes, D.L. Butler, E.S. Grood, R.F. Zernicke, and M.S. Hefzy. Biomechanical Analysis of Human Ligament Grafts used in Knee-Ligament Repairs and Reconstructions. The Journal of Bone and Joint Surgery, Vol. 66-A, 344-352, 1984.

F.R. Noyes, P.A. Mooar, D.S. Matthews, and D.L. Butler. The Symptomatic Anterior Cruciate-Deficient Knee. Part 1: The Long-term Functional Disability in Athletically Active Individuals. The Journal of Bone and Joint Surgery, Vol. 65-A: 154-162, 1983.

F.R. Noyes, D.S. Matthews, P.A. Mooar, and E.S. Grood. The Symptomatic Anterior Cruciate-Deficient Knee. Part II: The Results of Rehabilitation, Activity Modification, and Counseling on Functional Disability. The Journal of Bone and Joint Surgery, Vol. 65-A: 163-174, 1983.

The Orthopedic Clinics of North America: Symposium on The Anterior Cruciate Ligament, Part I. W.B. Saunders Co., J.R. Andrews and W.G. Carson, Jr., Guest Editors. Vol. 16, no.1 1985.

The Orthopedic Clinics of North America: Symposium on The Anterior Cruciate Ligament, Part II. W.B. Saunders Co., J.R. Andrews and W.G. Carson, Jr., Guest Editors. Vol. 16, no.2 1985.

Symposium: Application of Cell Culture in Toxicology, Fundamentals of Applied Toxicology, 6: 579-617, 1986.

Y. Tegner and J. Lysolm. Rating Systems in the Evaluation of Knee Ligament Injuries. Clinical Orthopedics and Related Research, 198: 43-49, 1985.

B. Zarins and C.R. Rowe. Combined Anterior Cruciate-Ligament Reconstruction using Semitendinosus Tendon and Iliotibial Tract. The Journal of Bone and Joint Surgery, 68-A: 160-177, 1986.