Guidance for Resorbable Adhesion Barrier Devices for Use in Abdominal and/or Pelvic Surgery; Guidance for Industry

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U.S. Department Of Health and Human Services
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Office of Device Evaluation

Plastic and Reconstructive Surgery Devices Branch
Division of General, Restorative and Neurological Devices
and
Obstetrics and Gynecology Devices Branch
Division of Reproductive, Abdominal and Radiological Devices

Preface

Public Comment

Comments and suggestions may be submitted at any time for Agency consideration to Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. When submitting comments, please refer to Docket No. 99D-5199 and the exact title of this guidance document. Comments may not be acted upon by the Agency until the document is next revised or updated.

For questions regarding the use or interpretation of this guidance, contact Elaine Blyskun at 301-796-6533 or by email at elaine.blyskun@fda.hhs.gov
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This document is intended to provide guidance. It represents the Agency's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind the Food and Drug Administration (FDA) or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute and regulations.

BACKGROUND

This guidance document discusses the development of preclinical and clinical information for an Investigational Device Exemption (IDE), Premarket Approval (PMA), or Product Development Protocol (PDP) application for a resorbable adhesion barrier product for use in the abdominal and/or pelvic cavity. This document provides guidance for the preparation of an IDE application and for the development of valid scientific evidence to support PMA applications for adhesion barriers that are resorbed within 30 days of placement into the peritoneal/pelvic cavity.

FDA has determined that the resorbable adhesion barrier is a significant risk device as defined in 21 CFR 812.3(m)(4). The resorbable adhesion barrier is a class III device which is subject to premarket approval in accordance with section 515 of the Federal Food, Drug, and Cosmetics (FD&C) Act.

This guidance document is based upon FDA's analysis of published scientific information, interaction with manufacturers, and input from FDA's Medical Device Advisory Committees (General and Plastic Surgery Devices Panel and the Obstetrics and Gynecologic Devices Panel). It is the product of a collaborative effort between the Plastic and Reconstructive Surgery Devices Branch (PRSB) in the Division of General Restorative and Neurological Devices (DGRND), and the Obstetrics and Gynecology Devices Branch (OGDB) in the Division of Reproductive, Abdominal, and Radiological Devices (DRARD). We encourage you to submit comments at any time. Please see the Preface of this document for instructions on submitting your comments.

Applications with primarily gynecologic indication(s) will be reviewed primarily by OGDB. Applications with more general abdominal indication(s) will be reviewed primarily by PRSB. Regardless which branch takes the lead role, there will be collaboration and consultation between the two branches. Appropriate reviewers from the Office of Device Evaluation (ODE), Office of Science and Technology (OST), Office of Surveillance and Biometrics (OSB), and Office of Compliance (OC) will participate in the review. Consultation from the Center for Drug Evaluation and Research (CDER) and/or the Center for Biologics Evaluation and Research (CBER) and appropriate device advisory panel members may be necessary depending on the product, indication(s) for use, conditions of use, and surgical models.

This guidance document provides a framework specific to the development of preclinical and clinical information for these devices. It is designed to be used in conjunction with other FDA

publications on IDE, PMA, and PDP applications. We cannot anticipate all of the issues related to individual products in a guidance document. Therefore, we encourage you to consult with FDA as early as possible in planning your product development.

The Least Burdensome Approach

The issues identified in this guidance document represent those issues that we believe need to be addressed before your device can be marketed. In developing the guidance, we carefully considered the relevant statutory criteria for Agency decision-making. We also considered the burden that may be incurred in your attempt to comply with the guidance and address the issues we have identified. We believe that we have considered the least burdensome approach to resolving the issues presented in the guidance document. If, however, you believe that there is a less burdensome way to address the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center web page at: http://www.fda.fgov/cdrh/modact/leastburdensome.html. You may send your written comments to the contact person listed in the preface to this guidance or to the CDRH Ombudsman. Comprehensive information on CDRH's Ombudsman, including ways to contact him, can be found on the Internet at: http://www.fda.gov/cdrh/resolvingdisputes/ombudsman.html.

GENERAL IDE REQUIREMENTS FOR ADHESION BARRIERS (21 CFR 812)

FDA has determined this device is a significant risk device as defined in 21 CFR 812.3(m)(4) and, therefore, studies involving these devices do not qualify for the abbreviated IDE requirements of 21 CFR 812.2(b). In addition to the requirement of having an FDA-approved IDE, sponsors of such trials must comply with the regulations governing institutional review boards (21 CFR 56) and informed consent (21 CFR 50).

Clinical evaluation of significant risk devices requires an approved Investigational Device Exemption (IDE) application in addition to IRB approval. The FD&C Act authorizes the FDA to exempt these devices from certain requirements of the Act that would apply to devices in commercial distribution. The exemption allows devices intended solely for investigational use to be shipped for use on human subjects during a clinical study.

An IDE application must, at a minimum, include the following elements:

- name of the device
- device description
- intended use
- report of prior investigations
- preclinical safety and effectiveness information
  - chemistry
  - animal testing for safety and effectiveness
  - physical, mechanical, and reliability testing
  - manufacturing
- clinical plan
  - purpose and objectives
  - study hypothesis

    - protocol
    - patient population
    - statistical considerations
    - risk/benefit analysis
    - product handling and storage information
- investigator information
- institutional review board (IRB) information
- sales information
- informed consent
- environmental impact
- other, e.g., case report forms
- labeling.

See 21 CFR 812 for these and additional IDE requirements.

GENERAL PMA REQUIREMENTS FOR ADHESION BARRIERS (21 CFR 814)

A PMA application must contain the following basic elements:

- name and address of applicant
- table of contents
- summary of safety and effectiveness:
    - indications for use
    - device description
    - alternative practices
    - marketing history
    - summary of studies (non-clinical and clinical)
    - conclusions drawn from studies
- complete description of:
    - device
    - components
    - properties relevant to adhesion prevention
    - principles of operation
    - manufacturing
- conformity to any applicable standards
- data
    - non-clinical
    - clinical
- bibliography
- labeling
- environmental assessment, unless the device qualifies for an exemption
- financial disclosure.

See also CFR 814.20 for additional information on these and other PMA requirements.

PRECLINICAL DATA

I. DEVICE DESCRIPTION

This section should identify the essential physical characteristic of the subject device, e.g., film, gel, solution. You should provide a detailed description of all features of the device, including the name of the device; physical dimensions (describe all sizes if applicable); all components; physical, chemical, and biologic properties; the mechanism(s) of action; and information regarding resorption and/or metabolism. You should also include a discussion of the scientific basis (physical/biologic plausibility), which supports the development of this product for this indication, with relevant scientific literature.

II. CHEMISTRY

A. You should describe **all** material components of the device. Such information should identify the source and purity of each component. You may supply the information by reference to a Master File(s), if you include the appropriate letter of cross-reference. Submission of a Certificate(s) of Analysis and/or a Materials Safety Data Sheet(s) (MSDS) can also greatly simplify review of components not commonly used in medical devices.

B. If collagen or other animal material is a device component, the application should identify the species and tissue from which the animal material was derived and the specific type of collagen or other material. See also the sterilization section below, on materials from animal sources, and the guidance document "Medical Devices Containing Materials Derived from Animal Sources (Except for In Vitro Diagnostic Devices) at: http://www.fda.gov/cdrh/ode/88.html.

C. You should submit the following information for each material/component in the device:

- chemical name, chemical abstracts service number
- trade name
- structural formula and molecular weight
- if the material is polymeric, you should provide the molecular formula, a measure of the average molecular weight, and the molecular weight distribution. FDA recommends measurement by gel permeation chromatography, but other techniques may be used
- if the product is solid, you should provide weight and dimensions per product unit
- if the product is liquid, you should provide weight, viscosity, color, and pH.

D. You should perform chemical characterization of each material to assess incoming material characteristics. The quality of the materials should be monitored for appearance, viscosity, average molecular weight, pH, organic volatile impurities, and

particulate matter as appropriate. You should list the incoming raw material specifications along with the test methods and appropriate limits of acceptance.

E. You should present the chemical formulation and manufacturing information in a step-by-step process, from the starting materials to final products. This should include all non-reactants and reactants (including catalysts, curing agents, and intermediate precursors) for all device components. You should include analyses of the copolymer content, when applicable, to establish the consistency of the product.

F. You should describe the finished sterilized device including the components and composition. You should document analytical tests and acceptance specifications with data from at least three lots compared and reported to demonstrate control over the manufacturing process.

G. Residual chemicals are a concern whether they are present as raw materials, as processed products of raw materials, or are introduced in any way during the manufacturing process. To address this concern, you should extract the final formulated sterilized product in both polar and non-polar solvents. You should measure potential toxic contaminants by a sufficiently sensitive method, such as High Performance Liquid Chromatography. You should also measure volatile and non-volatile residuals.

H. You should describe any unique characteristics of the device in sufficient detail using objective (quantitative) measures that will allow the reviewer a clear understanding of these unique characteristics.

III. ANIMAL TESTING

A. Toxicology/Biocompatibility Studies

The preclinical toxicology/biocompatibility studies should follow the ISO 10993-1: 1992 Guidelines, "Biological Evaluation of Medical Devices- Part 1: Evaluation and Testing," that recommends the six standard tests listed below for implanted devices that contact tissue for 24 h to 30 days with blood contact.

1. cytotoxicity
2. sensitization
3. irritation or intracutaneous reactivity
4. systemic toxicity
5. genotoxicity (ames reverse mutation, chromosomal aberration, and mouse lymphoma forward mutation)
6. subchronic implantation and toxicity

The subchronic implantation study duration should mimic the proposed use of the material. You should design the study with the characteristics of the product in mind; i.e., studies

should be carried out beyond the point of detectable levels of the product in the body. The test material should be implanted at or near the proposed site of use and should be assessed until after the material has been resorbed by the body. You should monitor the animals for systemic toxicity, as well as for local effects at the implantation site. You should also include macroscopic pathology and histopathology.

If the contact is longer than 30 days, we recommend chronic toxicity and carcinogenicity studies (i.e., 2-year rat implantation) as well.

General considerations for adhesion barriers

Safety margin -- In all biocompatibility and toxicity testing, the dose of the product used should reflect a reasonable safety margin compared to the doses proposed for use in humans. Generally, you should test a range of doses, up to ten times the highest dose to be used in humans, or provide a justification for a smaller safety margin. You should justify a human exposure larger than one-tenth of the no adverse effect level observed in animals.

Assessing biocompatibility of adhesion barriers -- The tests needed for assessing biocompatibility of adhesion barriers varies. For some materials, some tests may not be necessary, if you provide adequate justification. For other materials, additional tests may be necessary due to the nature of the material.

Preclinical testing -- You should complete all preclinical testing, with the possible exceptions of the carcinogenicity and reproductive and developmental toxicity testing, at the time you submit the IDE, prior to clinical use of the product. The exceptions will depend upon the results of the genotoxicity testing; the likelihood of reproductive or developmental effects; and the intended use of the device. Informed consent forms should disclose any safety studies that are pending. If the intended use is to improve fertility, the reproductive toxicology testing should be complete before patients are exposed to the barrier. As with the other aspects of this guidance document, you should direct specific questions to the appropriate reviewing division and branch.

Special considerations for adhesion barriers

Testing for Delay of or Prevention of Healing -- Inflammation and the replacement of soft tissue with fibrous tissue is an expected outcome of the normal healing process. Reducing the formation of adhesions may also delay or prevent healing. This should be tested in animal studies. Adhesion barriers placed at suture lines or at anastomotic sites should not reduce tissue-holding strength after suture removal.

Infectivity Testing – You should test enhancement of sepsis following challenge with a bacterial inoculum. This may result, for example, from the stimulation of bacterial growth, from the inhibition of antibiotic diffusion to the infection site, from a device-related increase in the entrance of infecting organisms into the systemic circulation from the surgical site, or from unknown mechanisms. You should challenge animals with a mixture of gut organisms in the presence and absence of the

adhesion barrier, and score for mortality and abscess formation. You should conduct studies with the appropriate sample size and design so as to be statistically valid.

Reproductive/Toxicology Studies – You should perform reproductive/developmental (teratology) toxicology studies using two species and evaluate the potential effects of the device on ovulation/spermiogenesis, conception, embryo-fetal toxicity, and teratological effects. You should design reproductive/developmental toxicity studies so that the maximum exposure of the product based on its ADME (see pharmacokinetics, below) occurs at the time of interest (ovulation/conception, early and late gestation).

Carcinogenesis/Metastasis Effects -- Device materials may have both local or systemic effects on the growth and/or metastasis of malignancies. FDA believes special testing is needed if the components of the barrier do not have a well-established history of implantation in the abdomen and pelvis, or if there is reason to suspect that one of the material components may effect the growth or metastasis of malignant cells. If the device is intended to be used in cancer patients, the preclinical testing should be followed by an oncology trial. Otherwise, the device should be contraindicated for patients with known or suspected malignancies.

B. Pharmacokinetics Studies

You should conduct pharmacokinetics studies to determine the absorption, distribution, metabolism and excretion (ADME) route(s), mechanism(s), and timeline of excretion of the product. If the product is metabolized or otherwise converted into molecular entities that may result in toxicity, the pharmacokinetics studies should address the fate of each of the toxic components over time. The studies should be carried out to time points at which there is no detectable level of the product. The studies should clearly address the fate of any toxic components identified in the chemistry section. Before the device is tested in humans, the pharmacokinetics or other data should demonstrate that any potential toxins do not pose a safety concern.

C. Effectiveness Studies

You should conduct effectiveness studies in appropriate animal model(s) to provide "proof of concept;" that is, these studies should suggest that there is a reasonable premise for efficacy in the human. Animal studies may also suggest better designs for the clinical studies to follow. These studies should represent, insofar as possible, the surgical approach (laparotomy versus laparoscopy), the specific surgical site(s) (e.g., between viscera and body wall, around loops of bowel), the types of adhesions (e.g., de novo adhesion formation versus reformation of existing adhesions), the method of adhesion evaluation (e.g., score, incidence, extent, severity), and the method of application that will be used in human studies.

They should also be well-designed and controlled to show statistically significant differences between group treated with the product and the control group. You should compare doses of the product to those proposed for use in humans. You should also include a brief discussion of the rationale for and the limitations of the animal model

used.

IV. PHYSICAL AND MECHANICAL TESTING

You should conduct bench testing of the physical/mechanical properties of the product and submit this information in the IDE application. The key physical properties of the device should be characterized. The actual testing will depend on the nature of the device. Solid, gel, and liquid barriers might be characterized by tear strength, cohesivity, or viscosity, respectively. At least one physical parameter should be used as a specification for the release of product.

V. MANUFACTURING

A. Product Characterization

Information about the product composition and structure is critical in precisely defining the device subjected to preclinical and clinical testing. Therefore you should include a full description of the device, including the physical dimensions, materials and properties of the product. Information similar to that discussed above in the chemistry section (i.e., reagent source, purity, certificate(s) of analysis, and/or MSDS) may be helpful in determining final product specifications.

You should identify each of the manufacturing, processing and packaging steps. You should present them in flow sheet form. Accompanying text should identify the purpose of each step, the components and materials used in each, as well as the quality control procedures and facilities used.

B. Final Product Specification

You should provide information about all in-process and final product tests. You should identify the product release specifications, test methods, sampling plans (including definitions of batch or lot), and acceptable quality levels.

You should select the final product release specifications to ensure that the product will perform safely and effectively. You should provide the rationale for the specifications. Examples of final product release specifications include the following:

- device dimensions
- composition of selected components
- mechanical properties
- residual levels of manufacturing reagents
- residual levels of heavy metals
- pyrogen levels
- sterility.

C. Product Expiration Dating

You should submit data supporting the expiration dating for the product. Stability studies should monitor the critical parameters of a device that are required to ensure the device will perform safely and effectively during its entire shelf-life, as described above under Final Product Specification (Section V. B.). You should provide justification for the tests selected. Studies should also demonstrate that sterility can be maintained over the shelf life of the device, either through sterility testing or package integrity testing.

You should collect the devices used for shelf life testing from at least three successive product lots; devices from each product lot should be evenly distributed among the groups of devices used for the various tests. The expiration date supported by the data should be the time at which there is at least a 95 percent probability that the selected parameter will be within the acceptance limit on the expiration date.

When accelerated aging studies are used to support shelf life, you should provide justification for the accelerated stress conditions. For example, decomposition mechanisms may show equivalence at both the standard and elevated temperatures, i.e., the slope of the Arrhenius curve is constant with changes in temperature. In cases where equivalence cannot be demonstrated, e.g., device failure occurs by different mechanisms at different temperatures, you should submit an additional justification.

You should verify the results of accelerated studies with real time test data.

D. Device Applicator

If a device applicator is used to apply the device, you should include a description of its design, function, and performance. If the applicator is cleared by 510(k), a brief description along with identification of the 510(k) are sufficient.

If the applicator is not cleared by 510(k), but is provided and designed exclusively for your adhesion barrier, then a more complete description is needed. If the applicator is reusable, see the guidance document, "Labeling Reusable Medical Devices Reprocessing in Health Care Facilities: FDA Reviewer Guidance" (April 1996), http://www.fda.gov/cdrh/ode/198.pdf. You may also obtain this guidance from the Division of Small Manufacturers, International and Consumer Assistance (DSMICA).

E. Sterilization

You should include the following information about product sterilization:

- the method of sterilization (e.g., ethylene oxide, irradiation)
- the validation method for the sterilization cycle
- the sterility assurance level (SAL) achieved (In general, a SAL of 10^{-6} is needed for all sterile devices, unless there is substantial justification for not being able to achieve this level.)

- the method for monitoring the sterility of each production lot
- a complete description of the packaging including the method of sealing the device.

If the method of sterilization is radiation, you should specify the dose. If the method of sterilization is ethylene oxide (EtO), you should identify the maximum levels of ethylene oxide and ethylene chlorohydrin residues that remain on the device. Residual levels of ethylene oxide and ethylene chlorohydrin that remain on the device following EtO sterilization should conform to the maximum limits for residual materials recommended in ANSI/AAMI/ISO 10993-7:1995, Biological Evaluation of Medical Devices - Part 7: Ethylene Oxide Sterilization Residuals (Sterility) (revised 8/20 1998) or to comparable methodology. The ANSI/AAMI/ISO document should be used with the accompanying AAMI Technical Information Report (TIR) No. 19:1998.

You should describe the aeration conditions and the time necessary for the product to reach the specified residual levels. You should also include a dissipation curve for the residual levels of ethylene oxide and ethylene chlorohydrin.

The document should also contain a complete description of the analytical methods that were used to qualify and validate the sterilization cycle for a disposable applicator and for the adhesion barrier itself. You should include copies of all protocols and raw data that support the validation of the sterilization cycle, including all calculations regarding the sterility assurance level.

You should identify the device bioburden and provide data to support the control of this bioburden during the production of the device. You should include copies of all protocols and raw data including identification of the portion of the device sampled for the testing. The application should also contain the results of bioburden resistance testing or a justification for why this is unnecessary. This testing should include devices tested from at least three manufacturing lots.

You should identify the time of routine revalidation and the circumstances (bioburden in excess of an established limit, or a change to the product, or packaging) that would necessitate revalidation of the sterilization cycle.

Materials from Animal Sources

For devices derived from animal material, FDA believes you need to demonstrate that the processing methods and sterilization techniques are sufficient to produce a SAL of 10^{-6}. The application should identify the species and tissue from which the material was derived. You should consult the CDRH Guidance, "Medical Devices Containing Materials Derived from Animal Sources (except for *in vitro* diagnostic devices): Guidance for Reviewers and Industry," http://www.fda.gov/cdrh/ode/88.html, for applicable information. For guidance on the viral safety of such products, see the "International Conference on Harmonization; Guidance on the Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin." This document can be

obtained from the Center for Biologics Evaluation and Research (CBER) at 1-888-CBER-FAX.

F. Pyrogenicity Testing

Pyrogenicity testing will help define limits to protect patients from the risk of febrile reaction. A febrile reaction to a pyrogenic substance may have the potential to increase the rate of adhesions. Testing by an established USP pyrogenicity assay such as the Bacterial Endotoxins Test (Monograph 85) using Limulus Amebocyte Lysate (LAL) or Rabbit Pyrogen Assay (Monograph 151) method ensures that the adhesion barrier device coming into contact with a patient has been tested for levels of gram-negative bacterial endotoxin present in the product.

You should identify the method of pyrogenicity testing, as well as information about how the assay was performed and the assay results. Because there is no "gold standard" in the medical community for what the upper limit of acceptability of endotoxin levels is for an adhesion barrier, it is important that you establish specification limits and manufacturing action levels and perform an established USP endotoxin test such as the Bacterial Endotoxin Test by LAL or Rabbit Pyrogen assay on any implanted device.

CLINICAL INVESTIGATIONAL PLAN

I. INTRODUCTION

This section provides points to consider when designing clinical protocols to support a PMA or PDP application for a resorbable adhesion barrier to be used in the peritoneal/pelvic cavity(s). While there is no consensus on a standardized clinical trial design for all of these devices, there are certain principles that FDA believes are essential for providing the valid scientific evidence needed to provide reasonable assurance of safety and effectiveness and bring these products to market. A clinical protocol for an adhesion barrier should include:

- clear statement of device's intended use
- clinical development plan designed to develop the data needed to support the intended use
- study hypothesis(es)
- study endpoints for safety and effectiveness
- plan for assessing safety in which all adverse events are identified and analyzed
- plan for assessing safety and effectiveness on the basis of an intent to treat population as well as an evaluable population
- assessment tools (e.g., adhesions scoring systems, planned second-look procedure, video, functional testing)
- study design with inclusion and exclusion criteria

- case report forms
- statistical methods
- risk/benefit analysis
- informed consent
- balance of premarket and post-approval data development
- labeling which accurately presents study data.

Note: We encourage you to work closely with FDA when developing study plans and protocols for these devices.

II. INTENDED USE

You should identify, as clearly and precisely as possible, the intended use of the adhesion barrier. The specific indications should include the following:

- adhesion type, i.e., de novo, reformed, surgical site, non-surgical site
- target population
- conditions for use
- anatomical site(s) of application
- expected outcomes.

These indications are commonly refined, as clinical experience from feasibility studies is analyzed. At the pivotal trial stage of product development, intended use, and indications should be in reasonably sharp focus.

The intended use determines the objectives of the clinical trial, which are generally to demonstrate the safety (i.e., associated morbidity and mortality) and effectiveness (i.e., associated patient benefit) of the device for a defined clinical benefit in a target population, under specific conditions of use.

The intended use should be clearly supported by data and be presented in the proposed labeling. Labeling in the clinical protocol should accurately present the data that have been collected on the device. One of the most difficult issues for adhesion barrier devices is how broad or narrow the indications should be, i.e., how much can the data from the clinical trials be extrapolated to broader or related uses. Part of the answer to this question depends on the selection of the surgical model(s) used in the trial and the ability of the sponsor or applicant to provide a sound scientific justification that the data support clinical benefit and safety in broader applications.

III. FEASIBILITY STUDIES

The purpose of feasibility (pre-pivotal) studies is to test the study methodology and to obtain preliminary clinical assessments of the safety and effectiveness of the device. These small, usually non-randomized, one or two center studies are intended to evaluate the procedures

that you will use in the pivotal study, refine the design of the device, refine the instructions for use, and provide initial experience to potential investigators. The data derived from feasibility studies are used to design the pivotal trial, estimating the treatment effect and sample size for the pivotal safety and effectiveness study.

Specific adhesion barrier device-related issues that you should address in pre-pivotal studies include:

- method of delivery and placement
- resorption and elimination in humans, if applicable
- site-to-site variability in the human body, if applicable
- effectiveness for various types of adhesions
- handling characteristics of the device
- target population
- conditions of use
- preliminary safety: morbidity and mortality effects; signs of increased infectivity and altered wound-healing
- sensitivity and specificity of assessment tools for detecting study endpoints and clinical benefit.

You should analyze the results of feasibility studies in a supplement to the IDE application before initiating the pivotal trial. We encourage you to schedule pre-pivotal meeting(s) with the FDA to present and discuss the results of these feasibility studies.

IV. PIVOTAL STUDIES

A. Purpose of Study

The purpose of a pivotal study is to develop the safety and effectiveness data to support the intended use, and therefore justify the indication(s) for use. The study purpose should clearly identify elements of the intended use: intent, target population, and conditions of use. Compound (multiple) intended uses should be addressed in separate statements for clarity. The broader the study is, the broader the eventual labeled indication for use may be.

B. Study Hypothesis

While the objective(s) provides a focus for the trial, the hypothesis is the basis for the statistical analysis. An effective and efficient clinical trial will have one or more objectives and corresponding hypotheses that are very specific and unambiguous. These objectives will answer a number of detailed questions about why the trial is being conducted including the following.

- Is the trial to show that a new device is as effective as, or better than another intervention or treatment? In other words, is the trial intended to support a claim of *equivalence* (non-inferiority) or *superiority*?

- How will effectiveness be judged?

- With respect to safety, is the trial intended to show that the new device is safer than, or as safe as, another treatment; and how will safety be evaluated?

- For which patients and condition will the device be used?

Answering these questions generally will provide the basis for the entire trial, as well as for labeling later. It is important you base testing of any statistical hypothesis(es) on clinically meaningful difference(s).

C. Endpoints

Based on the definition of effectiveness (21 CFR 860.7), the most direct method of providing valid scientific evidence of effectiveness is to select an appropriate clinical outcome and design a study to evaluate a statistically significant and clinically meaningful effect on a recognized adhesion-related morbidity. However, some clinical outcomes that result from adhesions may be difficult or impractical to evaluate in the premarket phase due to, for example, the multi-factorial nature of clinical outcomes such as live births or post-operative pain, or the overall low and time-dependent incidence of bowel obstruction due to post-operative adhesions. The clinical outcomes associated with adhesions may be reasonably assessed by parameters which are more immediately measurable and potentially less confounded.

In any case, clinical study outcomes endpoints should be:

- objective
- reproducible
- clinically reasonable/biologically plausible measures of clinical benefit for the target population.

Examples of clinically reasonable/biologically plausible measures are:

- validated multi-factorial scoring systems
- clinically meaningful incidence
- extent and severity of post-treatment adhesions in patients without adhesions at baseline
- clinically meaningful reduction in adhesion numbers
- extent and/or severity of post-treatment adhesions in patients with adhesions at baseline.

You may report incidence of observed adhesions in a number of ways, e.g., as the percentage of patients with no adhesions, or as the number of pre-designated surgical sites with adhesions. Extent and severity are also scored and reported in a variety of ways using a variety of different nomenclatures. Standardized composite scores of adhesions of predetermined grade at predetermined sites are being developed and utilized with increased frequency and should lead to greater reproducibility within and between studies.[1,2,3,6,7,9] For any scoring system, you should clearly define which anatomic sites are being scored. You should also define the following methods, if used in your scoring system:

- methods of evaluating extent of adhesions, i.e., direct measure with a centimeter marked ruler versus estimation of the percentage of organ covered;
- methods of evaluating the severity of adhesions; and
- methods of combining incidence, severity and extent scores into meaningful composite scores.

Currently, there is no consensus on the levels of adhesion reduction that are clinically significant. In addition, there is little information on the clinical significance of adhesion reduction at specific anatomical sites, or reduction of adhesion extent or severity.[4,5,11,12,14] You should carefully consider all of these parameters (level and sites of adhesion reduction) when designing a clinical trial. You should discuss clinical relevance of the extent of adhesion reduction indicated by your endpoints.

Post-approval studies are a reasonable method of further understanding the clinical relevance of the chosen endpoints. Post-approval studies are discussed below in section K.

D. Assessment Tools

The following tools for assessing adhesion reduction are being used now or, with some further development and testing, may be used in the future. We recognize that various tools have advantages and disadvantages. When choosing a method, the sponsor should discuss why this tool is appropriate for the study.

1. Second look surgery

Second look via laparotomy or laparoscopy is currently the primary modality for assessing adhesion formation/reduction in the abdomen and pelvis. It has the advantage of direct visual inspection; surgical manipulation to fully explore the cavity(s) and assess severity, e.g., filmy, firm, concrete; and provides an

opportunity for simultaneous therapeutic intervention. Issues that need to be addressed when second look is used include the following:

- the potential morbidity of a second surgical procedure unless planned in standard care;
- ethical issues regarding the potential benefit (or lack thereof) of such procedures to individual subjects;
- masking issues; and
- issues related to investigator bias.

2. Video recording

Video recording is frequently added to the second look assessment to provide a permanent record of the procedures and to provide a mechanism for masking by allowing for independent third party reviews. As with other technological advances, the utility of this methodology is highly dependent on the quality and reliability of the recording. Recordings should be complete and of sufficient optical quality to allow for accurate assessment of the quantity and quality of adhesions as well as an assessment of how those adhesions may be affected by the surgical exploration, itself. An important consideration when using video recording is that the method of evaluating the abdomen be consistent among patients (e.g., assessing surgical sites in the same order and for the same amount of time), in order to reduce potential bias.

3. Imaging studies

With additional technology development, imaging studies might be used in the assessment of adhesion barriers. Thus far, they do not provide enough detail to be used effectively in the abdomino-pelvic cavity.

4. Functional testing

Functional testing has shown great potential for assessing the impact of adhesion reduction in musculoskeletal applications; however, the present utility is less apparent for abdomino-pelvic applications. Newer methods for measuring intestinal motility and other methods of testing the function of gastrointestinal and gynecologic organ systems may be developed in the future to provide a useful, non-invasive alternative to surgically mediated anatomic assessment. These methods will require further research and validation.

E. Important Assessment Considerations

Because a consistent method of assessing adhesion reduction has not been established, you should include detailed information about the following in your clinical protocol:

- anatomic sites to be evaluated;
- the time during surgical procedure at which adhesion scoring will be done (beginning or end or both in case of partial or selective adhesiolysis);

- adhesion characteristics to be measured (incidence, severity, extent) and methods of grading or measuring each characteristic;
- method of assessing each component of the score at each anatomic site, e.g., laparoscopic, open laparotomy, videotaping;
- method of counting an anatomic site that is to be evaluated but is anatomically not present or not assessable in a specific patient;
- methods of combining the adhesion characteristics per anatomic site, per patient, or per treatment group; and
- methods for establishing that the composite score (when used) is a valid and reliable tool for assessing adhesions or the morbidity resulting from adhesions.

F. Study Design

1. Control

FDA recommends randomized, concurrently-controlled, pivotal trials, given the absence of well-defined historical controls or other appropriate control methods. You should justify your choice of control with the most recently available, peer-reviewed literature.

2. Randomization

Randomization should occur immediately prior to device application, after a patient has been evaluated and found to satisfy pre-operative, as well as intra-operative inclusion / exclusion criteria. The time of randomization should be documented on the case report form.

3. Masking

You should address, to the greatest extent possible, the potential for investigator and, to a lesser degree, patient bias. Investigator masking is problematic for adhesion barrier trials that use either placebo or active controls, since differences between the test and control subjects are usually readily apparent and it is normally preferable, from a patient care perspective for the same surgeon to perform the initial and second look procedures. You may use one of several alternative methods for controlling bias including video recording with masked independent review or application of the device/control by an assistant who will not participate in adhesion scoring. You should assess these or other methodologies during the feasibility (pre-pivotal) phase of development.

4. Patient Selection Criteria

The target population should consist of patients who are expected to benefit from device use under specified conditions of use. The inclusion and exclusion criteria for the clinical study should identify significant patient variables that characterize the target population, such as:

- age
- sex
- fertility status
- pregnancy history
- history of abdomino-pelvic disease due to adhesions, e.g., recurrent bowel obstruction, infertility, pain
- adhesion burden at baseline, e.g., none, mild, moderate, severe with objective and definition of mild, moderate, severe
- surgical history
- history of inflammatory disease
- history of major organ dysfunction
- surgical wound classification[10]: clean, clean-contaminated, contaminated, or dirty.

You should identify intraoperative inclusion/exclusion criteria prospectively. Some exclusions, such as active pelvic infection, fecal contamination, unexpected malignancy, and extent of adhesions, may not be known until the time of surgery. You should consider excluding patients undergoing certain unanticipated surgical procedures, such as the removal of a fallopian tube or ovary, because such procedures may complicate the adhesion count. Randomization should not occur until the time the device or control is placed.

5. Procedure

You should include information about the following in your description of the clinical procedure in which the adhesion barrier device is used:

- when, where, and how the device is used
- minimum and maximum dosage per patient
- length of procedure
- method of lysis
- possible covariates, e.g., blood loss, glove use.

6. Follow-up

You should prospectively define the period of follow-up and frequency/content of evaluations. These should be appropriate for the device, procedure, and the endpoint you are evaluating. Please see the discussion of post-approval studies in section K, below for further information.

G. Statistical Methods

You should provide a comprehensive statistical plan. It should include prospectively defined methods of addressing each of the following:

- study hypothesis
- sample size calculation
- number of study centers
- success/failure criteria
- effectiveness patient populations (intent-to-treat, evaluable, etc.)
- pooling of data
- covariates
- stratification
- protocol deviations
- drop-outs
- analysis plan and statistical methods
- data auditing.

1. Analysis Cohorts

The "Intent-to-Treat" population, which is defined to be the cohort of all enrolled and treated patients, is the preferred population for study outcome analysis. Intent to Treat analysis allows for the evaluation of all patients who enroll in the study, even though some may not complete the study, e.g., patients who are, for any reason, lost to follow-up, drop-outs, or terminated by investigator. You should prospectively specify the analysis plans that will account for patients who do not complete the study. You should also present analysis of the "Evaluable" patient cohort, i.e., patients who enter and complete the study, recognizing such analyses are subject to bias. Comparison of outcomes on the basis of Intent to Treat and Evaluable patients allows assessment of outcome robustness. Analysis details should be prospectively agreed upon by the sponsor and FDA.

2. Data Poolability

Most clinical trials are conducted at more than one study site, but the sample size for the study assumes that results from all the study sites may be combined or *pooled*. Many times, this assumption is warranted. However, sometimes it is not. Thus, investigating whether study results may be pooled across study sites will be a key element of the analysis.

Poolability is both a clinical and a statistical issue. If there are clinically important differences in the way the trial was done at different sites, then instead of a single trial at multiple sites, there is actually a series of single center trials that need to be assessed and presented separately. In the same way, statistically significant differences in results at study sites indicate that there is an important inconsistency

among the study sites that should be investigated, and not lost in an overall finding. Differences among sites may be important indicators of critical issues in device performance. For example, exploring the reasons for observed differences may uncover training, learning curve issues, or special labeling concerns.

A simple approach to investigating poolability has three steps.

1. A clinical assessment of the way the trials were done at the study sites. Clinically meaningful differences here may preclude pooling.

2. A statistical/clinical assessment to evaluate the similarity of patient characteristics and baseline measurements. Differences here may indicate poolability problems. At the very least, these differences will indicate the need for a more complex statistical analysis.

3. A statistical analysis testing the consistency of results across study centers. Again, differences here may indicate poolability problems or the need for a more complex statistical analysis.

When testing for differences among sites, the absence of statististically significant differences does not indicate that data can be pooled, because most trials are sized for an assessment over all sites. For this reason, clinically meaningful differences (even statistically non-significant ones) should not be ignored, but instead should be investigated.

One approach to investigating statistical variation among sites is to use a statistical model that includes site, along with other factors. If the analysis confirms that site is important, results should be presented by site. If a statistically significant interaction between site and treatment occurs, it indicates a major inconsistency among the sites, which should be investigated.

3. Covariates

Covariates, or potentially confounding variables, may significantly compromise the ability of the sponsor and the agency to adequately analyze the data from clinical trials. You should avoid procedural variations, such as the use of different doses, different methods of application, different surgical tools, different gloves, etc., whenever possible. You should accurately record all variables, such as whether Lactated Ringer's or other instillates were left in the abdomen or completely or partially removed.

You should address major differences in surgical approach, such as laparotomy vs. laparoscopy and the inclusion of multiple surgical procedures with vastly different adhesiogenic potential, in separate studies or by prospectively designed stratification plans.

You should identify and control for co-morbidities that may confound evaluation of device effect. Inclusion/exclusion criteria should address the presence or absence of diseases (e.g., active pelvic infection), the severity of the diseases, and historical information. Patients excluded from the study will, in general, also be excluded in the labeling for the approved product.

You should control for other variables known or suspected to be confounding, e.g., the use of anti-inflammatory medications, by appropriate randomization, inclusion/exclusion criteria, by evaluation in separate study arms, by stratification, or by a prospectively designed covariate analysis.

4. Additional Information

Additional information on study design and statistical analysis issues are available from CDRH, in the guidance document entitled, "Statistical Guidance for Clinical Trials of Non-Diagnostic Medical Devices," www.fda.gov/cdrh/ode/ot476.html. The Center's Division of Biostatistics prepared this guidance with input from ODE, academia, and the medical device community.

H. Case Report Forms

You should design case report forms to capture all pertinent information at each point in the study from patient screening, through patient enrollment, the initial treatment period, assessment of adhesions, and all other patient follow-up. You should maintain a screening log for both the pilot and pivotal studies to allow assessment of reasons for non-enrollment of patients considered for the trial.

For operative procedures the case report forms should record variables (covariates) that could potentially confound the endpoints, such as:

- the presence of foreign bodies resulting from powder from unwashed gloves, gauze, or paper towels
- procedure duration
- estimated blood loss
- the number and locations of adhesions lysed
- the types of adhesion, e.g., *de novo* or reformed
- Surgical Wound Classification[10]: clean, clean-contaminated, contaminated, dirty.

I. Device Applicators

You should describe any device applicator used with the adhesion barrier product in the clinical protocol, and provide information about the training investigators and practitioners receive. If the applicator is not cleared by 510(k), and it is provided with and designed exclusively for your adhesion barrier, then FDA may consider the

applicator part of the device, and include it in evaluating the safety and effectiveness of the device.

J. Informed Consent

The requirements for all patients for informed consent, adequate monitoring, and necessary records and reports are given in 21 CFR Parts 50, 56, and 812. Patients should be clearly informed of, among other things, the following:

- the safety and effectiveness of the new device has not been established
- adhesions may actually worsen with treatment
- adhesions may cause or worsen morbidity such as female infertility or pain
- adhesions may prevent or reduce morbidity such as obstructive anastomotic leak
- the incidence of small bowel obstruction due to post-laparotomy adhesions is approximately 5%.

Women who desire fertility, should be excluded from feasiblity studies or warned that the effects of the device on fertility have not been defined.

K. Post-approval Studies

There are several reasons why you may conduct a post-approval study. In some cases, FDA may require you to conduct a post-approval study as a condition of PMA approval. FDA might require a post-approval study to follow up on unresolved safety issues, such as infection rates, where incidence rates are too low for the pivotal study to accurately predict. Or, FDA might require a post-approval study to provide further understanding of a finding from the pivotal study that is not completely explained by the available data.

FDA typically relies on input from the advisory panel when requiring a post-approval study.

Moreover, you may choose to conduct additional studies on your approved device in order to address limitations in the approved labeling, to provide additional information for interested clinical users of the device, or to provide additional information to third party payers.

L. Special Considerations

1. Laparotomy versus Laparoscopy

Generally, you should evaluate adhesion barriers separately in laparotomy and laparoscopic surgical models.[8,13] Data derived from laparotomy studies may not accurately predict efficacy when extrapolated to a laparoscopic model, because significant quantitative and qualitative differences may occur in adhesion formation depending on whether the surgery is done by laparoscopy or laparotomy.

2. Malignancy

For adhesion barrier devices intended to be used in the presence of known or newly discovered malignancy, you should anticipate the need for additional preclinical and clinical testing focused on the issues of accelerated tumor growth and impact on clinical progression of primary and metastatic disease. You should discuss specific protocols with the reviewing division before initiating one of these trials.

V. RISK/BENEFIT ANALYSIS

Reasonable assurance of safety and effectiveness is based upon a scientific analysis of risk/benefit. In order to perform such an analysis it is critical, as discussed above, that you collect complete, objective, and unbiased data for both safety and effectiveness for FDA's review. FDA and its advisory panels will perform its own independent risk/benefit analyses.

We encourage you to provide, both in the IDE and PMA, risk/benefit analyses that accurately characterizes your product in a way that would allow prospective users to make an informed decision regarding its use. The risk/benefit analysis for the PMA will be more definitive, because it will include the results of the clinical trial(s). The risk/benefit analysis should be based on your in-depth knowledge of your device, data, and the science of adhesion formation and prevention. It is important that this analysis be as data-based and objective as possible.

The risk analysis should identify all of the known and potential risks of the use of the device. It should include risks attendant to the procedure(s) involved in the trials, as well those risks directly attributable to the use of the product. These risks should be analyzed separately and in combination. You should also describe your plans to recognize, understand, and minimize the risks.

The benefits analysis should identify potential benefits to the patient. It should include any information available about likely differences in benefits to different patient populations.

VI. LABELING

Investigational devices must be labeled in accordance with 21 CFR 812.5 and in accordance with 21 CFR 812.5, they must state: "CAUTION – Investigational Device. Limited by Federal (or United States) law to investigational use."

In the PMA, the final marketing labeling should contain the following basic elements:

- brief device description
- indications for use
- contraindications
- warnings/precautions
- adverse events
- clinical studies

- patient information (as needed)
- instructions for use.

A. Indications for Use

Labeling should accurately represent the data that has been collected on the device. The label indication should be based on the studies conducted to support that indication. You should prospectively define the expected indications as clearly and specifically as possible. The indications will depend upon the selection of the surgical model(s) used in the trial. See also the section entitled Clinical Investigational Plan, II. Intended Use.

B. Contraindications

This section should list those circumstances under which the device should never be used. For example, if an adhesion barrier was known, based on animal or human data, to increase infectivity, it would be contraindicated in the presence of active infection or enteral contamination.

C. Warnings/Precautions

When increased risk or decreased benefit is anticipated based on available information or not adequately evaluated based on study design (inclusion/exclusion criteria), such factors should be listed in this section. Examples include:

- Decreased effectiveness should be expected in the presence of less than meticulous hemostasis.

- The safety and effectiveness of this product has not been evaluated during pregnancy.

- The safety and effectiveness of this product with respect to its effect on the ability to conceive has not been evaluated.

D. Adverse Events

You should clearly present all adverse events recorded in the clinical trials in tabular form, including numbers and percents. You should list adverse events in a meaningful sequence based upon incidence rates, severity, or another relevant paradigm. You should describe deaths and other significant adverse events in both text and tabular form.

E. Clinical Studies

Clinical studies on which safety and effectiveness are based should be summarized in tables of data that include the following:

- patient accountability
- demographics
- procedure variables
- baseline evaluation of effectiveness endpoints
- follow-up evaluation of effectiveness endpoints
- follow-up evaluation of safety endpoints

Conclusions and interpretations should be objective.

F. Instructions for Use

You should provide detailed instructions that reflect the experience gained in preclinical and clinical studies. These instructions should include:

- device preparation
- patient preparation
- device delivery
- device application
- dosing recommendations
- operative technique
- post-operative care
- retreatment (if applicable).

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