

Guidance for Industry and/or for FDA
Reviewers/Staff and/or Compliance

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

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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of Device Evaluation**

**Plastic and Reconstructive Surgery Devices Branch
Division of General and Restorative Devices**

**Obstetrics and Gynecology Devices Branch
Division of Reproductive, Abdominal, and Radiological Devices**

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Preface

Public Comment:

For 90 days following the date of publication in the Federal Register of the notice announcing the availability of this guidance, comments and suggestions regarding this document should be submitted to the Docket No. assigned to that notice, 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.

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

REGULATORY BACKGROUND	2
INTRODUCTION	3
GENERAL IDE REQUIREMENTS FOR ADHESION BARRIERS	3
GENERAL PMA REQUIREMENTS FOR ADHESION BARRIERS	4
PRECLINICAL DATA	5
I. Device Description	5
II. Chemistry	5
III. Animal Testing	6
A. Toxicology/Biocompatibility Studies.....	7
B. Pharmacokinetic Studies	8
C. Performance Studies	8
IV. Physical and Mechanical Testing	8
V. Manufacturing	9
VI. Sterilization	10
CLINICAL INVESTIGATIONAL PLAN	11
I. Introduction	11
II. Intended use	12
III. Feasibility Studies	12
IV. Pivotal Studies	13
A. Purpose of Study.....	13
B. Hypothesis	13
C. Endpoints	14
D. Assessment Tools	16
E. Study Design	17
F. Statistical Methods	18
G. Informed Consent.. ..	20
H. Special Considerations.....	20
I. Case Report Forms	21
J. Device Applicators	21
K. Postmarket Studies	21
V. Risk/Benefit Analysis	21
VI. Labeling	22
REFERENCES	24

*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 FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

REGULATORY BACKGROUND

The purpose of this document is to provide guidance to manufacturers of resorbable adhesion barrier products for use in the abdominal and/or pelvic cavities. This guidance discusses the development of preclinical and clinical information in the context of an Investigational Device Exemption (IDE) application and Premarket Approval (PMA). A Product Development Protocol (PDP) application may also be used. More information on this option may be found at the CDRH Internet site www.fda.gov/cdrh/pdp/pdpguide.pdf.

This guidance document is based upon FDA's analysis of published scientific information, interaction with manufacturers, and input from our Medical Device Advisory Committee (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) of the Division of General and Restorative Devices (DGRD), and the Obstetrics and Gynecology Devices Branch (OGDB) of the Division of Reproductive, Abdominal, ENT, and Radiological Devices (DRAERD). This guidance should be viewed as a "living" document and, as with all device-specific guidance, it is expected that periodic updates will be necessary, to reflect what is learned about these products over time. Constructive commentary is encouraged from all interested parties at any time.

This guidance document provides a framework specific to the development of preclinical and clinical data for PMA/PDP applications for resorbable adhesion barrier products intended for use in the peritoneal cavity. It is designed to be used in conjunction with other FDA publications on IDE, PMA, and PDP applications and should not be construed as a replacement for these documents. Sponsors are encouraged to consult with FDA as early as possible in the course of formulating their product development plans. Although the use of this document to prepare preclinical and clinical protocols is not mandatory and cannot anticipate all of the issues related to individual products, it is hoped that by providing an overview of agency expectations, this guidance will reduce unnecessary work for sponsors and allow for a more efficient FDA review.

FDA regulations cited herein are in the Code of Federal Regulations, Title 21, as follows:

- Premarket Approval of Medical Devices (21 CFR 814)
- Investigational Device Exemptions (21 CFR 812)
- Determination of Safety and Effectiveness (defines valid scientific evidence) (21 CFR 860.7)
- Protection of Human Subjects; Informed Consent (21 CFR 50)
- Institutional Review Boards (21 CFR 56)
- Good Laboratory Practice (GLP) Regulations (21 CFR 58)
- Environmental Impact Considerations (21 CFR 25)
- Quality System Regulation (21 CFR 820)
- Product Development Protocol (Section 515(f) of Food Drug and Cosmetic Act and Guidance on the Content of a Product Development Protocol)

All FDA publications referred to in this guidance document can be obtained by contacting the Division of Small Manufacturers Assistance (DSMA) at 800-638-2041 (toll free) or 301-443-6597. Some publications can be obtained via the CDRH Internet site at www.fda.gov/cdrh/dsmamain.html. Specific questions and clarification regarding this guidance document should be directed to PRSB at 301-594-3090.

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INTRODUCTION

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. Resorbable adhesion barriers are Class III devices which are subject to pre-market approval in accordance with section 515 of the Food Drug and Cosmetics (FD&C) Act. Clinical trials utilizing these devices are considered significant risk and therefore subject to all provisions of the IDE regulation.

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.

Applications for adhesion barriers for use in the abdomen will be reviewed by the Obstetrics and Gynecology Devices Branch in the Division of Reproductive, Abdominal, ENT, and Radiological Devices, or the Plastic and Reconstructive Surgery Devices Branch in the Division of General and Restorative Devices. Regardless of which division and branch takes the lead role, there will be collaboration and consultation between the two branches as needed, and participation of 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). Also, consultation from the Center for Drug Evaluation and Research (CDER) and/or the Center for Biologic Evaluation and Research (CBER) and appropriate device advisory panel members may be obtained depending on the product, indication(s) for use, conditions of use, and surgical models.

GENERAL IDE REQUIREMENTS FOR ADHESION BARRIERS (21 CFR 812)

An IDE application should, 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

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- Investigator information
- IRB information
- Sales information
- Informed Consent
- Environmental Impact
- Other, e.g., case report forms.
- Labeling

See also 21 CFR 812 for these and additional IDE requirements. In addition, several guidances are available on CDRH's website in the Index under "Investigational Device Exemptions (IDEs)" at <http://www.fda.gov/cdrh/indexgk.html#1>.

GENERAL PMA REQUIREMENTS FOR ADHESION BARRIERS (21 CFR 814)

A PMA application should 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 Diagnosis or Treatment
 - Principles of Operation
 - Manufacturing
- Conformity to Any Applicable Standards
- Data
 - Non-clinical
 - Clinical
- Bibliography
- Labeling
- Environmental Assessment
- Financial Disclosure
- Other Information as Requested

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

A PDP application should contain the information as described in the agency's Guidance on the Content of a Product Development Protocol.

PRECLINICAL DATA

I. DEVICE DESCRIPTION

This section should identify the essential physical characteristic of the subject device, e.g. film, gel, solution, etc. 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 should be provided. A discussion of the scientific basis (physical/biologic plausibility) which supports the development of this product for this indication should also be included, with relevant scientific literature.

II. CHEMISTRY

- A. All material components of the device should be described. Such information should identify the source and purity of each component. The information may be supplied by reference to a Master File(s), if the appropriate letter of cross-reference is included. Although not sufficient for a comprehensive review of the chemistry of a product, submission of a Certificate(s) of Analysis and/or a Materials Safety Data Sheet(s) (MSDS) can also be helpful for the review of components not commonly used in medical devices.
- B. If animal material (e.g., collagen) is a device component, the application should also identify the species and tissue from which the animal material was derived and the specific type of material. Special considerations may be necessary, including how processing methods and sterilization techniques will reduce the level of viruses below an infectious level. Review of the ICH Draft Guideline on Viral Safety Evaluation of Biotechnology Products from Cell Lines of Human or Animal Origin is recommended with regard to the design of such studies and the selection of model viruses. In addition, guidance entitled “Medical Devices Containing Materials Derived from Animal Sources (Except for *in vitro* Diagnostic Devices): Guidance for FDA Reviewers and Industry,” at <http://www.fda.gov/cdrh/ode/88.html> should be consulted.
- C. For each material/component in the device, the following information is requested:
- Chemical Name, Chemical Abstracts Service number.
 - Trade Name
 - Structural Formula and weight
 - If the material is polymeric, the molecular formula, a measure of the average molecular weight, and the molecular weight distribution should be provided. Measurement by gel permeation chromatography is preferred, but other techniques may be used.
- D. Chemical characterization of each material should be performed to assess incoming material characteristics. Appropriate tests may include, e.g., Fourier Transform Infrared Spectroscopy, mass spectroscopy, carbohydrate or amino acid analysis for chemical identification. The quality of the materials should be monitored for appearance, viscosity, average molecular weight, pH, organic volatile impurities, and particulate matter as

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appropriate. Incoming raw material specifications should be listed with test methods and appropriate limits of acceptance.

- E. Chemical formulation and manufacturing information should be presented 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. Analyses of the copolymer content should be included, when applicable, to establish the consistency of the product.
- F. The finished sterilized device (see Section V.E. for sterilization information) should be described including the components and composition. Analytical tests and acceptance specifications should be documented 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 in raw materials, or as processed products of raw materials, or are introduced in any way during the manufacturing process. To address this, the finished sterilized product in its final formulation should be extracted in both polar and non-polar solvents. Potential toxic contaminants should be measured by a sufficiently sensitive method, such as High Performance Liquid Chromatography (HPLC). Volatile and nonvolatile residuals also should be measured.
- H. Any unique characteristics of the device should be described in sufficient detail using objective (quantitative) measures to allow the reviewer a clear understanding of these unique properties.

III. ANIMAL TESTING

In all biocompatibility and toxicity testing, the amount of the product used should reflect an appropriate safety margin compared to the doses (on a milligram per kilogram basis) proposed for use in humans. Generally, doses at least ten times the highest dose to be used in humans should be tested.

The tests assessing biocompatibility of adhesions barriers may vary. Some tests may not be necessary if adequate justification is provided by the sponsor, or additional tests may be necessary due to the nature of the material.

Generally, all preclinical testing, with the possible exceptions of the chronic and carcinogenicity (if applicable) and reproductive and developmental toxicity testing, should be completed before the submission of the IDE, prior to clinical use of the product. Exceptions will depend upon the results of the completed biocompatibility/toxicology and pharmacokinetic studies, the likelihood of reproductive/developmental effects and the intended use of the device. Informed consent forms should disclose current and pending safety data (e.g., any chronic toxicity, reproductive and developmental toxicology or carcinogenicity testing). 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, specific questions should be directed to the appropriate reviewing division/branch.

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A. Toxicology/Biocompatibility Studies

Preclinical toxicology/biocompatibility studies such as the ones listed below should be conducted. The ISO 10993-1: 1992 Guidelines, "Biological Evaluation of Medical Devices- Part 1: Evaluation and Testing," recommend the following standard tests for implanted devices contacting tissue for 24 h to 30 days:

1. Cytotoxicity
 2. Sensitization
 3. Irritation or Intracutaneous Reactivity
 4. Systemic Toxicity
 5. Genotoxicity (Ames Reverse Mutation, Chromosomal Aberration, Sister Chromatid Exchange and Mouse Lymphoma Forward Mutation)
 6. Subchronic Implantation and Toxicity.
- The subchronic implantation study duration should mimic the proposed use of the material. The test material should be implanted at or near the proposed site of use. Evaluation should continue until after the material has been resorbed by the body. The animals should be monitored for systemic toxicity, as well as for local effects at the implantation site. Macroscopic pathology and histopathology should be included.
 - If the contact is longer than 30 days, chronic toxicity and carcinogenicity studies (i.e., 2-year rat implantation) are also recommended.

Special Considerations for adhesion barriers:

1. Testing for Delay of or Prevention of Healing -- Inflammation and the replacement of soft tissue with fibrous tissue are expected outcomes of the normal healing process. Reducing the formation of adhesions therefore may delay or prevent healing. This may be true at sites of incision or anastomosis, or at areas denuded of peritoneum. Delayed healing should be evaluated using histopathology in animal studies.
2. Testing for Enhancement of Infection -- Enhancement of local infection or sepsis may result from the stimulation of bacterial growth, the inhibition of antibiotic diffusion to the infection site, from a device-related increase in the permeability of infecting organisms into the systemic circulation, or from unknown mechanisms. This might be tested by challenging animals with a mixture of gut organisms in the presence and absence of the adhesion barrier, and scored for mortality and abscess formation. Studies should be conducted with the appropriate sample size and design so as to be statistically valid.
3. Reproductive/Toxicology Studies -- These studies should be performed using two species and should evaluate the potential effects of the device on ovulation/spermiogenesis, conception, embryo-fetal toxicity, and teratological effects. Reproductive/developmental toxicity studies should be designed so that the maximal exposure of the product based on its ADME (see pharmacokinetics,

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below) occurs at the time of interest (ovulation/conception, early and late gestation).

4. Tumor Growth/Metastasis Effects -- Device materials may have an effect on the growth and/or metastasis of malignancies, both locally and systemically. Therefore, preclinical studies will be needed to address this potential, if it is to be used in cancer patients. The effects on tumor growth and metastasis should be assessed before the device is tested in a clinical oncology trial. In the absence of testing in an oncology trial, the product will be contraindicated for patients with known or suspected malignancies.

B. Pharmacokinetics Studies

Pharmacokinetic studies should be conducted 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 broken down into smaller molecular components, then the pharmacokinetic studies should address the fate of each of the components over time. The studies should be carried out to time points beyond 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.

C. Performance Studies

Performance studies should be conducted in the appropriate animal model(s) to provide “proof of concept;” that is, these studies should suggest that there is 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, etc.), 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 the group treated with the product and the control group. Doses of the product should be compared to those proposed for use in humans. A brief discussion of the rationale for and the limitations of the animal model used should be included.

IV. PHYSICAL AND MECHANICAL TESTING

Bench testing of the physical/mechanical properties of the product should be conducted and submitted 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

For guidance additional to that noted here, please refer to “Guidance on Quality System Regulation Information for Various Premarket Submissions,” at <http://www.fda.gov/cdrh/comp/qsrpma.html> .

A. Product Characterization

Information about the product composition and structure is critical in precisely defining the device subjected to preclinical and clinical testing.

A full description of the device, including the physical dimensions, materials and properties of the product, should be included. 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.

Each of the manufacturing, processing and packaging steps should be identified and presented 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

The sponsor should provide information about all in-process and final product tests. Such data should identify the test method and time of testing during manufacture. The release criteria should be compared with the levels at which effectiveness is reduced. Examples of final product release specifications can include the following:

- Device dimensions
- Composition
- Mechanical properties
- Residual levels of manufacturing reagents
- Residual levels of heavy metals
- Sterility (see Section V.E. below)
- Pyrogen levels (see Section V.F. below)
- Levels of adhesion reduction in an animal model associated with these specifications.

C. Product Expiration Dating

Data supporting the expiration dating for a product should be submitted. Such data should be collected from at least three successive product lots. Stability studies should monitor the critical parameters of a device to assure safe and effective device performance during its entire shelf-life. The incidence of in-vivo adhesion reduction should be used, as well as the other final product specifications.

The appropriateness of accelerated stability data is determined by device composition. The value of accelerated stability test data relies on equivalent decomposition pathways at

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both the standard and elevated temperatures. Therefore, in situations where device failure occurs by different mechanisms at the standard and elevated temperatures of accelerated stability testing, (e.g., loss of sterility at 25⁰ C and protein denaturation at 50⁰ C), accelerated stability test data should not be used to support claims for product stability. In addition, accelerated stability test data may only be used to extend product expiration dating for six months beyond the date demonstrated by real time stability testing. If real time data support an expiration date of 12 months, then an expiration date of 18 months is appropriate as long as accelerated stability test data support this.

D. Device Applicator

If a special or designated applicator is to be used when applying the device, a complete description of its design, function, and performance should be included.

E. Sterilization

The following information should be included with respect to product sterilization (see further details below the bullets):

- The method of sterilization (e.g., ethylene oxide, irradiation, etc.);
- The validation method for the sterilization cycle;
- The sterility assurance level (SAL) to be achieved. In general, a SAL of 10⁻⁶ is recommended 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 device used to seal the device parameters.

If radiation is the sterilization method used, the dose should be specified. If the method of sterilization is ethylene oxide (EtO), the maximum levels of ethylene oxide, ethylene chlorohydrin residues that remain on the device should be identified. Residual levels of ethylene oxide and ethylene chlorohydrin which remain on the device following EtO sterilization should comply with the maximum limits for residual materials pursuant to 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 always be used with the accompanying AAMI Technical Information Report (TIR) No. 19:1998.

The information should contain a description of the aeration conditions and the time necessary for the product to reach the specified residual levels and 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 any applicator and for the adhesion barrier itself. Copies of all protocols and raw data that support the validation of the sterilization cycle, including all calculations regarding the sterility assurance level should be included.

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The device bioburden should be identified and data supporting the control of this bioburden during the production of the device provided. Copies of all protocols and raw data including identification of the portion of the device sampled for the testing should be included. The submission should also contain the results of a bioburden resistance testing or a justification for why this is unnecessary. This testing should include a representative sampling of the manufacturing lot(s).

The time of routine revalidation should be identified, as should 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.

If a reusable applicator is supplied with the adhesion barrier, see the guidance document, "Labeling Reusable Medical Devices Reprocessing in Health Care Facilities: FDA Reviewer Guidance" (April 1996). This guidance may be obtained from the Division of Small Manufactures Assistance (DSMA).

F. Pyrogenicity Testing

Pyrogenicity testing will help define limits to protect the 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.

The method of testing should be identified, 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 the manufacturer establish specification limits, manufacturing action levels and performs 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 that may support a premarket approval application (or PDP) for a resorbable adhesion barrier to be used in the peritoneal/pelvic cavity(ies).

- A clear statement of intended use
- A clinical study plan designed to develop the data needed to support the proposed intended use
- An appropriate study hypothesis(es)
- Appropriate study endpoints (effectiveness)
- A plan for assessing safety in which all adverse events are identified, documented and analyzed

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- Appropriate assessment tools (e.g. second-look, video, functional testing)
- Appropriate study design
- Appropriate statistical methods
- A risk/benefit analysis
- Appropriate balance of premarket and postapproval data development
- Labeling which accurately reflects study data

Note: Sponsors are strongly encouraged to work closely with FDA when developing study plans and protocols.

II. INTENDED USE

The sponsor should identify, as clearly and precisely as possible, the intended use of the adhesion barrier. The specific indications, i.e., type of adhesion (de novo, reformed, surgical site, distal), target population, conditions for use, anatomical site(s) of application, and the expected clinical outcomes at each site should be clear. One way to refine these parameters is through the clinical experience gained from feasibility studies. By the time the sponsor has reached the stage of a pivotal clinical trial, the intended use and indication(s) should be well-focused.

The intended use determines the trial objectives, 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 purpose in a target population, under specific conditions of use.

Labeling should accurately reflect the data which has been collected on the device. One of the most difficult issues with respect to 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 to provide a sound scientific justification for applying the data to a broader range of applications. For example, a device which shows efficacy in reducing adhesions between liver and colon could with reasonable certainty be expected to show similar results between spleen and stomach. Applying this same data to an efficacy claim for the reduction of interloop small bowel adhesions may be less convincing.

III. FEASIBILITY STUDIES

The purpose of feasibility (pre-pivotal) studies is to obtain preliminary clinical assessments of the safety and effectiveness of the device. These small, usually non-randomized, one or two site studies are intended to evaluate the procedures to be used in the pivotal study, refine the design of the device, refine 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 establishing the appropriate sample size for the pivotal safety and effectiveness study. Feasibility studies are recommended when there is no other clinical experience with the adhesion barrier, in order to refine clinical study parameters before the pivotal study. Specific adhesion barrier device-related issues that can be addressed in pre-pivotal studies include:

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- Method of delivery and placement
- Resorption and elimination in man
- Site to site variability
- Effectiveness for various types of adhesions
- Handling characteristics of the device.
- Dose response
- Signs of increased infectivity and altered wound-healing

The results of any feasibility studies should be presented prior to commencement of a pivotal trial. Pre-pivotal meetings with the agency, where these data are presented and discussed, are encouraged.

IV. PIVOTAL STUDIES

A. Purpose of Study

The purpose of the study should be clearly stated. Examples of representative statements of purpose may include:

- To evaluate the safety and effectiveness of the device for preventing and/or reducing adhesions of the pelvic sidewalls and cul-de-sac in premenopausal women following ovarian surgery
- To evaluate the safety and effectiveness of the device for reducing adhesion formation in the peritoneal cavity following intestinal surgery
- To evaluate the safety and effectiveness of the device for preventing de novo surgical site adhesions following upper abdominal (hepatic, splenic, gastric) surgery
- To evaluate the safety and effectiveness of the device for preventing and/or reducing adhesions, including de novo and reformed, surgical-site and distal, of the abdomino-pelvic cavity

Note: In general, the broader the study is, the broader the eventual labeled indication for use will be. Please see the Endpoints section for a more detailed discussion of surrogate endpoints.

B. Hypothesis

The study hypothesis reflects what the sponsor expects the study to show. Examples of study hypotheses (expressed in plain English) for adhesion barriers may include:

- Placement of the device between the uterine incision and the surrounding viscera will reduce the number of patients experiencing chronic pain following a myomectomy to 75% that of the control group of equal size during the 12-month follow-up period.
- The use of the device at the anastomotic site in patients undergoing colectomy for Crohn's disease will reduce the number of patients suffering small bowel obstruction by 75% compared to meticulous surgical technique alone, during the five years following the surgery.

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- The use of the device in laparoscopic surgery as an adjunct to adhesiolysis to reduce pelvic adhesion reformation in infertile patients, will increase the viable pregnancy rate to twice that seen in the control group during the two years following the surgery.
- The use of the device will triple the number of patients with no adhesions between the uterus and surrounding structures at second-look laparoscopy as compared with patients treated with lactated ringers alone, following myomectomy performed by laparotomy.
- In patients with endometriosis, the use of the device at surgical sites (of endometriosis removal) will reduce the adhesion rate to one third that of the control group in which meticulous surgical technique alone is used.

The examples are given to illustrate the detailed kinds of statements that adequately define the purpose of the study.

C. Endpoints

Optimally, endpoints should directly address clinical outcome measures (e.g., decreased infertility, pelvic pain or bowel obstruction). Because of the difficulty in assessing some clinical endpoints in the premarket phase due either to the length of time needed for such a study, or the larger number of patients needed to assess less common events, validated surrogate endpoints which are based on quantitative, reproducible, objective measures may sometimes be used. Examples include validated multi-factorial scoring systems, clinically meaningful increase in patients without adhesions, clinically meaningful reduction in numbers, extent and/or severity of adhesions).

1. Clinical endpoints

The most direct method of providing valid scientific evidence of effectiveness is to select an appropriate clinical endpoint(s) and design a study that may demonstrate a statistically significant and clinically meaningful effect on recognized adhesion-related morbidity.

Clinical endpoints of interest with respect to abdominal adhesions are bowel obstruction, chronic abdominal pain, and increased morbidity or technical difficulty with reoperative surgery (laparotomy and/or laparoscopy). Due to the low incidence and extended timeline for bowel obstruction; and the multifactorial causes of surgical complications; the assessment of clinical outcome measures in the premarket period may be problematic.

Similarly, clinical endpoints of interest in gynecology, including fertility and pelvic pain are complex and difficult to study due to a large number of confounding variables which are hard to control for.

Notwithstanding these acknowledged impediments, sponsors are encouraged to directly assess clinical endpoints whenever possible.

2. Surrogate endpoints

A surrogate endpoint is a laboratory measurement or a physical sign that is substituted for a clinical endpoint. Surrogate endpoints tend to be easier to measure and quantify, may require a shorter study duration, and decrease the cost of clinical trials. When considering the use of surrogate endpoints it is necessary to consider:

- Biologic plausibility
- Reproducibility
- Clinical validation

Currently there is no consensus on the level of adhesion reduction that is clinically significant, and little information on the clinical significance of adhesion reduction at specific anatomical sites, or reduction of adhesion extent or severity^{4,5,10,11,13}. Therefore, when designing a clinical trial that uses adhesion scoring systems, careful consideration should be given to the clinical relevance of these parameters.

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}. Analytic methods to verify the reliability of whatever assessment tools are selected to measure surrogate endpoints should be prospectively incorporated into the clinical trial design.

Incidence may be reported in a number of ways, e.g., as the percentage of patients with no adhesions, or as the percentage of pre-designated surgical sites with no adhesions. Extent and severity are also scored and reported in a variety of ways using a variety of different nomenclatures. The method of determining the endpoints for a pivotal study should take into consideration the following:

- Which anatomic sites and how many anatomic sites should be scored;
- 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.

In addition, the expected treatment effect (e.g., 50% overall reduction of adhesions at specified anatomical sites) should be clearly identified prospectively.

Clinical validation of the surrogate endpoint is also needed. Reference to published peer reviewed validation studies which are related to the intended use of the device may be sufficient; however, such studies are lacking for many of the indications currently being sought by manufacturers. When appropriate literature studies are not available, sponsors should include a surrogate validation component as part of their pivotal study. See the Section on Postmarket Studies for further discussion of this point.

D. Assessment Tools

Because a consistent method of assessing adhesion reduction has not been established, the following information should be specified in all clinical trial protocols:

- Anatomic sites to be evaluated;
- The time during surgical procedure at which adhesion scoring will be done (beginning or end).
- 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.

The following tools have been identified for assessing adhesion reduction. 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** 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. Disadvantages of second look include the morbidity of a second surgical procedure, ethical issues regarding the lack of potential benefit of such procedures to individual subjects, masking issues, and issues related to investigator bias.
2. **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 independent third party reviews to read videos blinded at a later time. The value of this is highly dependent on the quality 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. When using video recording the method of evaluating the abdomen should be consistent for all patients, assessing surgical sites in the same order and for the same amount of time, in order to reduce potential bias.
3. **Imaging** studies have, thus far, not been used effectively in the assessment of adhesion barriers in the abdomino-pelvic cavity. As the quality of abdominal imaging improves, this may change, eliminating the need for surgical second look

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and expanding the options for investigators with respect to surgical models and study designs.

4. The utility of **functional** testing, which has shown great potential for assessing the impact of adhesion reduction in musculoskeletal applications, is less apparent for abdomino-pelvic applications. Newer methods for measuring intestinal motility and the function of gastrointestinal and gynecologic organ systems may provide a useful, non-invasive alternative to surgically mediated anatomic with further research and validation.

E. Study Designs

1. Control

Controlled trials are strongly recommended given the absence of well-defined historical controls. Sham or active controls such as Lactated Ringer's or other legally marketed adhesion barriers may be considered. In addition, depending on the formulation of an adhesion barrier, it is possible that a patient may, serve as their own control.

2. Randomization (Treatment Assignment)

Randomization should be used to minimize the introduction of bias into the study. After a patient has been found to satisfy both pre-operative as well as intra-operative inclusion/exclusion criteria, and the surgery has been completed, treatment assignment can occur immediately prior to device application. The time of randomization relative to surgery and device application should be prospectively planned and clearly documented on the case report form.

3. Masking

The potential for investigator and patient bias should be addressed to the greatest extent possible. The feasibility of using the following or other methodologies should be assessed early in the clinical study plan. There are several possible approaches for masking, including, but not limited to, the following:

- Investigator masking. This may occur if a control product is the same in appearance as the treatment product, or if the investigator is absent during application of the treatment product. Investigator masking may be problematic for adhesion barrier trials using either placebo or active controls since differences between the test product and control may be readily apparent.
- Switching to a second surgeon for the second look procedure. A disadvantage to this method is that patients may prefer the same surgeon to perform the initial and second look procedures.
- Independent review of the videotape. Care should be taken to ensure that the videotape recordings are of sufficient quality to allow consistent and accurate scoring of adhesions.

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4. Patient Selection Criteria

This section should include the inclusion and exclusion criteria. Preoperative inclusion/exclusion criteria should identify significant patient variables such as:

- Age
- Gender
- Fertility status
- Pregnancy history
- Pelvic/abdominal disease history, e.g. recurrent bowel obstruction
- Surgical history

Intraoperative inclusion/exclusion criteria should also be defined 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. The exclusion of patients undergoing certain unanticipated surgical procedures such as the removal of a fallopian tube or ovary should be considered, because such procedures may complicate the adhesion count. For these reasons, it is recommended that randomization should not occur until just before the device or control is to be placed.

5. Follow-up

The period of follow-up and frequency/content of evaluations should be prospectively defined and appropriate for the device, procedure, and the endpoint being evaluated. Please see the discussion of postmarket studies on page 23 for further information.

F. Statistical Methods

A comprehensive statistical plan should be provided in the protocol addressing the following aspects of the clinical study and data analysis:

- Sample size calculation
- Number of study sites
- Success/failure criteria
- Stratification
- Statistical procedures and analysis
- Patient spreadsheet
- Potential confounding variables
- Pooling of data
- Protocol deviations
- Drop-outs
- Data auditing

A critical component of a successful IDE or marketing application is the use of appropriate statistical measures to design and analyze studies to provide valid scientific

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evidence in support of specific device claims. Some study design issues have been raised elsewhere in this document, and there is also a general statistical guidance available from CDRH, entitled, “Statistical Guidance for Clinical Trials of Non-Diagnostic Medical Devices.” The Center’s Division of Biostatistics has prepared this guidance with input from ODE, academia, and the medical device community. The guidance may be obtained at www.fda.gov/cdrh/ode/ot476.html, or calling the Division of Biostatistics at 301-594-0616.

Parametric and Nonparametric Methods:

There is a great deal of data that can be best described as having real clinical meaning, but lacking specific mathematical properties that allow this data to be evaluated using traditional parametric statistical measures. Parametric measures presume a number of underlying assumptions regarding the data and how it is distributed. Moreover, parametric measures are designed to analyze data that is at least interval in nature - that is, has a fixed and meaningful unit of measure, and at least an arbitrary zero point. Much of the data that is meaningful from a clinical perspective, with respect to adhesion scoring, is ordinal data - that is, the information has direction and magnitude, but no clear fixed unit of measure, or true zero point. Some other examples of this type of information include classifications of disease such as the New York Cardiovascular Index, patient or physician rating scales, quality of life indices, etc. Analyzing data that fails to meet the underlying assumptions of a parametric approach, or analyzing ordinal data with these techniques may result in equivocal analyses and conclusions, or worse.

Non-parametric statistical methods may provide powerful alternative techniques that are appropriately used in analyzing ordinal data or even interval or ratio data in cases where the basic parametric assumptions, such as a normal distribution of data, may not be completely met. These measures are powerful and efficient statistical techniques, but have fewer and more general assumptions. They are especially valuable in analyzing clinical signs, quality of life issues, other relevant rating scales, and can be used in survival analysis as well. CDRH encourages the appropriate use of non-parametric techniques in situations where these techniques are clearly indicated, or in cases where the underlying assumptions of traditional parametric measures may be questionable. The sponsor is encouraged to meet with appropriate ODE and statistical staff early in the planning process to discuss the potential use of non-parametric measures.

Confounding variables:

Confounding variables may significantly compromise the ability of the sponsor and the agency to adequately analyze the data from clinical trials. Procedural variations such as the use of different doses, different methods of application, different surgical tools, different gloves, etc. should be avoided whenever possible. All variables should be accurately recorded such as whether, in the use of Lactated Ringer’s or other instillates, they are left in the abdomen or completely or partially removed.

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

Co-morbidities that may confound evaluation of device effect should be identified and controlled for. 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.

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

G. Informed Consent

The requirements for the informed consent for all patients, adequate monitoring, and necessary records and reports are listed in 21 CFR Parts 50, 56, and 812. Patients should be clearly informed, among other things, that the safety and effectiveness of the new device has not been established and that adhesions may actually worsen with treatment. Women who desire fertility should be excluded from preliminary studies or warned that the effects of the device on fertility have not been defined.

H. Special Considerations

1. Laparotomy versus laparoscopy

Products should, in general, be evaluated separately for laparotomy and laparoscopic surgical indications^{8,12}. Sponsors are encouraged to develop laparoscopic animal models to estimate efficacy of laparoscopic use prior to initiation of human laparoscopic trials (see Animal Testing section). Due to significant differences, both quantitative and qualitative, in adhesion formation following laparoscopic procedures as opposed to similar procedures performed via laparotomy, data derived from laparotomy studies may not be fully extrapolated to predict efficacy in the laparoscopic model. It is anticipated, however, that existing laparotomy data could be referenced to reduce the data supporting a subsequent laparoscopic indication.

2. Malignancy

For adhesion barrier devices intended to be used in the presence of known or newly discovered malignancy, sponsors 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. Specific study protocols should be discussed with the reviewing division prior to initiation of these trials.

I. Case Report Forms

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Case Report Forms should be designed to capture all pertinent information at each point in the study from patient enrollment, through the initial treatment period, subsequent second look procedures, and all other patient follow-up.

For operative procedures the case report forms should record potentially confounding procedural variables, 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
- risk classification, e.g., clean, clean, clean contaminated, versus dirty (e.g., see Schwartz *et al.* Principles of Surgery, 7th edition, pp. 130 – 136 (1999).
- in the second look surgery, the type of adhesion, e.g., *de novo* or reformed

J. Device Applicators

Any device applicator used with the adhesion barrier product should be fully described in the clinical protocol, and information regarding the training investigators and practitioners in its use should be provided. Unless an approved device is used, the applicator will be considered part of the device, and will be part of the safety and effectiveness evaluation of the barrier.

K. Postmarket Studies

FDA may require studies as a condition of approval of a PMA or PDP (see 21 CFR § 814.82 for additional details on postmarket studies). Sponsors may also choose to perform studies to attempt to remove limitations in labeling, provide additional information to prospective users, provide additional information to third party payers, etc.

V. **RISK/BENEFIT ANALYSIS**

Determination of safety and effectiveness is based upon an analysis of risk/benefit. In order to perform such an analysis it is critical that complete, objective, and unbiased data for both safety and effectiveness be collected and reviewed. The agency and its advisory panels will perform their own independent risk/benefit analyses.

Sponsors are encouraged to provide, both in the IDE and PMA, risk/benefit analyses which accurately characterize their product in a way that would allow prospective users to make an informed decision regarding its use. A risk/benefit analysis should be performed which identifies all of the known and potential risks of the use of the device. This 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 should be analyzed separately and in combination. Plans to recognize, understand and minimize the risks should also be described.

VI. LABELING

Investigational devices must be labeled in accordance with 21 CFR 812.5. It must contain, “CAUTION – Investigational Device. Limited Federal (or United States) law to investigational use.”

In the marketing application, the proposed 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
- Prescription Use statement (“Caution: Federal law restricts this device to sale by or on the order of a physician.”)(21 CFR Section 801.109(b)(1)).

A. Indications for Use

Labeling should accurately reflect the data that has been collected on the device. A device’s labeled indication for use should be based on the studies conducted to support the indication. Although labeling will be refined based on the data generated during clinical studies, sponsors should prospectively define the expected indication(s) for use as clearly and specifically as possible. For a further discussion of indication(s) for use, see Section II (“Intended Use”) under Clinical Investigational Plan.

B. Contraindications

This section should list those circumstances under which the device should *never* be used. One example might be that adhesion barrier devices which are known, based on animal or human data, to enhance infectivity, should not be used 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 may 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.

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

D. Adverse Events

All adverse events (AEs) recorded in clinical trials should be clearly presented in tabular form including number and percent. Events should be listed in a meaningful sequence based upon incidence rates, severity, or another relevant paradigm. Deaths and other significant AEs should be described in paragraph form.

E. Clinical Studies

Clinical studies on which safety and effectiveness are based should be summarized with as much of the data presented in tabular form as is practical. Inflated conclusions and interpretations should be avoided.

F. Instructions for Use

Detailed instructions which reflect the experience gained in preclinical and clinical studies should be provided, and should include:

- Device preparation
- Patient preparation
- Device delivery
- Device application
- Dosing recommendations
- Operative technique
- Post-operative care
- Retreatment (if applicable)

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