

## **A. General Overview of the Investigational Device Exemption (IDE) Review Process**

An investigational device exemption (IDE) allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data required to support a Premarket Approval (PMA) application or a Premarket Notification [510(k)] submission to FDA. Investigations covered under the IDE regulation are subject to differing levels of regulatory control depending on the level of risk. The IDE regulation distinguishes between significant and nonsignificant risk device studies and the procedures for obtaining approval to begin the study differ accordingly. Also, some types of studies are exempt from the IDE regulations.

### **Significant Risk Device**

A significant risk device presents a potential for serious risk to the health, safety, or welfare of a subject. Significant risk devices may include implants, devices that support or sustain human life, and devices that are substantially important in diagnosing, curing, mitigating or treating disease or in preventing impairment to human health. Examples include cardiac pacemakers, hydrocephalus shunts, and orthopedic implants. The Cardima Revelation Tx Microcatheter and NavAblator System is considered a significant risk device.

### **IDE Application**

In addition to obtaining institutional review board (IRB) approval for their study, a sponsor of a *significant risk* device study must submit a complete IDE application to FDA. There are no preprinted forms for an IDE application; however, an IDE application must include certain required information, most notably a report of prior clinical, animal, and laboratory testing of the device as well as the proposed investigation plan for the study being requested. It should be noted that it is the responsibility of the sponsor to design and propose an appropriate clinical study. The sponsor must demonstrate in the application that there is reason to believe that the risks to human subjects from the proposed investigation are outweighed by the anticipated benefits to subjects and the importance of the knowledge to be gained, that the investigation is scientifically sound, and that there is reason to believe that the device as proposed for use will be effective.

### **FDA Action on IDE Applications**

FDA may approve, conditionally approve, or disapprove an IDE application. FDA may also request additional information about an investigation prior to rendering a formal decision. An explanation of the possible actions is given here.

### Disapproval of an IDE

FDA may disapprove or withdraw approval of an IDE application if there is reason to believe that the risks to the human subjects are not outweighed by the anticipated benefits to the subjects or the importance of the knowledge to be gained, that informed consent is inadequate, that the investigation is scientifically unsound, or that the device as used is ineffective.

### Conditional Approval of an IDE

In the event FDA has concerns or questions unrelated to patient safety or the scientific soundness of the investigation, the Agency may issue a conditional approval for an IDE. This includes sending a letter to the company that identifies FDA's remaining concerns, which need to be addressed within 45 days of the date on the letter. In other words, the *final* protocol does not need to be established prior to FDA granting conditional approval if the sponsor has provided adequate safety information to the Agency.

After receiving conditional approval, the sponsor is permitted to begin their investigation assuming they have obtained IRB consent. However, if they choose to begin enrolling patients without addressing or resolving the issues, questions or "future concerns" (see below) included in the conditional approval letter, they do so at their own risk.

Conditional approval letters also include a general statement that FDA approval of an IDE application does *not* [emphasis added] imply that the investigation will develop sufficient safety and effectiveness data to assure FDA approval of a premarket approval (PMA) application for the device under study.

### Approval of an IDE

If, after FDA has reviewed a sponsor's request to begin or change a clinical investigation, and there are no remaining concerns with the sponsor's proposal related to patient safety or the scientific soundness of the study, or any other aspects of the application, FDA will approve the IDE.

As with conditional approval letters, there is a general statement that approval of an IDE application does not imply that the investigation will develop sufficient safety and effectiveness data to assure FDA approval of a premarket approval (PMA) application for the device under study.

### Future Concerns

It is possible that FDA will include *future concerns* (sometimes referred to as "advisory statements," or "below-the-line items") in an IDE approval or conditional approval letter. In doing so, FDA cautions the sponsor to give serious consideration to certain concerns listed which we believe are considered important for the future presentation or analysis of their data for the purposes of determining safety and effectiveness for a PMA application.

## **B. General Overview of the Premarket Approval (PMA) Review Process**

Premarket approval (PMA) is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices. Class III devices are those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury. Due to the level of risk associated with Class III devices, FDA has determined that general and special controls alone are insufficient to assure the safety and effectiveness of class III devices. Therefore, these devices generally require a premarket approval (PMA) application under section 515 of the Food Drug & Cosmetic (FD&C) Act in order to obtain marketing clearance.

PMA is the most stringent type of device marketing application required by FDA. The applicant must receive FDA approval of its PMA application prior to marketing the device. PMA approval is based on a determination by FDA that the PMA contains sufficient valid scientific evidence to assure that the device is safe and effective for its intended use(s). An approved PMA is, in effect, a private license granting the applicant (or owner) permission to market the device. The PMA owner, however, can authorize use of its data by another.

### **Review of the PMA Application**

The review of a premarket approval application (PMA) is a four-step review process consisting of:

- Administrative and limited scientific review by FDA staff to determine completeness (filing review);
- In-depth scientific, regulatory, and Quality System review by appropriate FDA personnel;
- Review and recommendation by the appropriate advisory committee (panel review); and
- Final deliberations, documentation, and notification of the FDA decision.

#### Filing a PMA (21 CFR. 814.42)

The filing of an application means that FDA has made a threshold determination that the application is sufficiently complete to begin an in-depth scientific review. Within 45 days after a PMA is received by FDA, the Agency will notify the applicant whether the application has been filed. The decision to file is acknowledgement that the sponsor has provided an *administratively* complete submission. The decision to file a PMA can and is made prior to any substantial review of the data contained within the application. The letter will include the PMA reference number and the date FDA filed the PMA.

Expedited review status, if requested, applicable, and granted, will be communicated at this time. The date of filing is the date that a PMA accepted for filing was received by the Agency. The 180-day period for review of a PMA starts on the date of filing.

#### In-depth review (21 CFR 814.44)

FDA will begin substantive review of the PMA after it is accepted for filing (§814.42). During the review process, FDA will notify the PMA applicant via major/minor deficiency letters of any information needed by FDA to complete the review of the application.

If the applicant on their own initiative or at FDA's request submits a PMA amendment (§814.37) which contains significant new data from a previously unreported study, significant updated data from a previously reported study, detailed new analyses of previously submitted data, or significant required information previously omitted, the review period may be extended up to 180 days.

#### Panel Review (21 CFR 814.44)

FDA may refer the PMA to an outside panel of experts (advisory committee). In general, all PMAs for the first-of-a-kind device (such as the Cardima Revelation Tx System) are taken before the appropriate advisory panel for review and recommendation. The PMA, or relevant portions, may be forwarded to each member of the appropriate FDA advisory committee for review. During the review process, FDA may communicate with the applicant [§814.37(b)] or with the advisory committee to respond to questions that may be raised by committee members or to provide additional information to the panel. FDA maintains a record of all communications with the applicant and with the advisory committee.

If the PMA is referred to an advisory committee, the committee must hold a public meeting to review the PMA in accordance with 21 CFR 14. The advisory committee must submit a final report to FDA that includes the committee's recommendation and the basis for such recommendation on the PMA. The advisory committee report and recommendation may be in the form of a meeting transcript signed by the chairperson of the committee. The advisory panel is tasked with providing one of three recommendations to the Agency for a given marketing application: Full Approval, Approval with Conditions, or Disapproval. The threshold for approval is that the data has provided a reasonable assurance of safety and effectiveness.

FDA takes into consideration the transcript of the meeting, the panel's recommendation, and other information in reaching a final decision on the PMA. FDA informs the applicant whether FDA agrees with the panel's recommendation or disagrees and what additional information is needed from the applicant (in the event of an approvable or not approvable decision). If the application is approvable, the applicant must agree to the "Conditions of Approval."

## **FDA Action on PMA Applications**

### Approval Order

**Recommendation:** Approval (valid scientific evidence has been provided to demonstrate that the device is reasonably safe and effective)

After FDA reviews the committee's final report, the FDA will issue an order to the applicant that the PMA is approved if none of the reasons in §814.45 (Denial of approval for a PMA) for denying approval of the application applies. FDA will approve an application on the basis of draft final labeling. Approval will be based on the condition that the applicant submits to FDA a copy of the final printed labeling before marketing. FDA will notify the public of the approval. The announcement of the decision and the availability of a summary of the safety and effectiveness data (SSED) on which the decision is based will be published on the Internet. The summary will include information about any adverse effects of the device on health. When a notice of approval is published, data and information in the PMA file will be available for public disclosure in accordance with §814.9.

### Approvable Letter

**Recommendation:** Conditional Approval (all issues of safety and effectiveness have been addressed, but additional information is necessary to complete the application)

FDA will send the applicant an approvable letter if the application substantially meets the requirements of the FD&C Act, and FDA believes that it can approve the application if specific additional information is submitted or specific conditions are agreed to by the applicant. The approvable letter will describe the information that FDA requires to be provided by the applicant or the conditions that the applicant is required to meet to obtain approval. FDA may require, for example, as a condition of approval:

- The submission of certain information identified in the approvable letter, such as final draft labeling;
- An FDA inspection that finds the manufacturing facilities, methods, and controls in compliance with the Quality System regulations (21 CFR 820) and, if applicable, verification of records pertinent to the PMA;
- Restrictions imposed on the sale, distribution, or use of the device under section 515(d)(1)(B)(ii) or 520(e) of the FD&C Act; or
- Post-approval requirements.

With this option, the applicant will need to agree to perform a post-approval study, or agree with the restrictions on prescription use or restrictions on the training of individuals who may use the device before approval. The applicant may also be notified of required postmarket surveillance and/or tracking requirements.

### Not approvable letter

***Recommendation:*** Not Approvable (valid scientific evidence has not been provided to demonstrate that the device is reasonably safe and effective)

FDA will send the applicant a not-approvable letter if FDA believes that the application may not be approved or if FDA is unable to reach an approvable decision due to a lack of significant information in the application. The not-approvable letter will describe the deficiencies in the application, including each applicable ground for denial. Where possible, FDA will identify what is necessary to make the PMA approvable (e.g. recommend that new prospective clinical data be provided).

In response to a not approvable letter, the applicant may:

- Amend the PMA as requested by FDA;
- Request administrative review by filing a petition for reconsideration (21 CFR 10.33); or
- Withdraw the PMA.

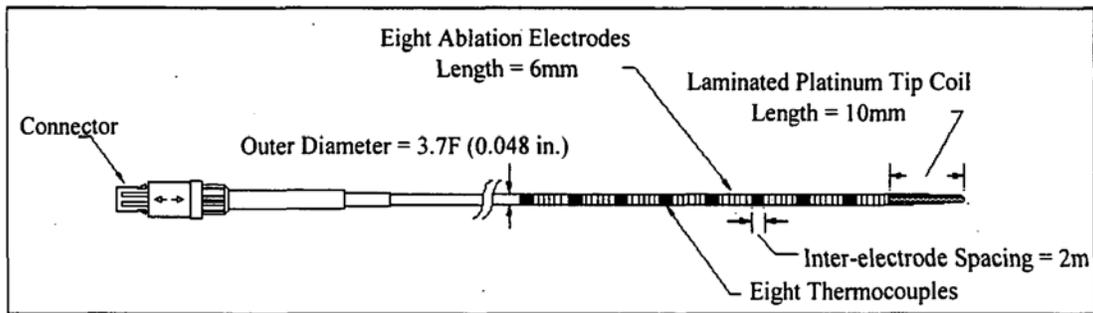
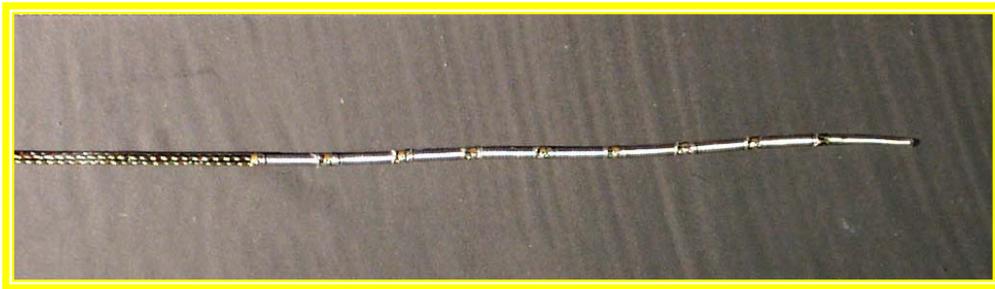
FDA will consider a PMA to have been withdrawn voluntarily if:

- The applicant fails to respond in writing to a written request for an amendment within 180 days after the date FDA issues such a request;
- The applicant fails to respond in writing to an approvable or not approvable letter within 180 days after the date FDA issues such a letter; or
- The applicant submits a written notice to FDA that the PMA has been withdrawn.

## Design of Revelation Tx Microcatheter

The Revelation Tx Ablation Microcatheter (3.7 F) is a single use, steerable, non-deflectable, multi-electrode microcatheter with a flexible, non-electrically active tip. It has eight electrodes and eight thermocouple temperature sensors on the distal end of the catheter in a linear array for feedback control of RF energy. Radiofrequency energy is applied to each electrode individually. This catheter is designed for the treatment of atrial fibrillation by creating linear lesions. The legally marketed Naviport Guiding Catheter is a deflectable guiding catheter with sizes ranging from 8F to 11F used to aid in the positioning of the Revelation Tx.

The relatively thin Revelation Tx catheter is intended to produce thin “linear” lesions to simulate the right atrial linear MAZE surgical procedure. The small, flexible design is intended to facilitate vascular access and is proposed to reduce the risk of navigation in and around the atrial chamber. The catheter electrodes are configured along the surface of the distal end (but not the tip). It is this longitudinal configuration of electrodes that are intended to permit the creation of linear lesions.



**Figure 1.** (Top) Photograph of Revelation Tx Microcatheter; (Bottom) Engineering Diagram of Revelation Tx Microcatheter

## Revelation Tx design vs. other approved catheters

Unlike "conventional" endocardial RF ablation catheters, the REVELATION Tx is intended to provide a more flexible and less traumatic interface with endocardial tissue at its distal tip. The Revelation Tx has eight coiled electrodes and eight thermocouple temperature sensors on the distal end of the catheter. Each electrode uses the thermocouple just proximal to the electrode for temperature feedback control of RF energy in order to maintain a pre-selected thermocouple-sensed set temperature.

	<b>Revelation Tx Microcatheter</b>	<b>“Conventional” RF ablation catheters</b>
<b>Electrodes</b>	8 coiled ablation electrodes, 6mm in length each	Typically a single ablation electrode, 4-5 mm in length
<b>Steerable</b>	Requires use of a guiding catheter	Typically are steerable without the use of a guiding catheter
<b>Gauge</b>	3.7F	7F, 8F
<b>Catheter Tip</b>	Non-electrically active tip	Ablation electrode at catheter tip

The literature suggests that these long narrow electrode designs, such as with the Revelation Tx, may be associated with increased coagulum formation on the electrodes (please refer to the References section of the panel pack). Radiated energy concentrates at sharp geometric gradients called the “edge effect”, which may explain the increased coagulum formation. Therefore, the power and temperature distributions from long electrode designs may differ from those of standard ablation catheters. Coagulum and char formation can be improved by utilizing dual-edge temperature sensors rather than single temperature sensors, such as the single thermocouple per electrode design of the Revelation Tx.

**SUMMARY OF APPROVED PMAS FOR PERCUTANEOUS CATHETER ABLATION**

**Study Design Comparison**

	<b>Sponsor</b>	<b>Rhythm</b>	<b># patients</b>	<b>Study design</b>	<b>Objective procedural endpoint</b>	<b>Objective chronic endpoint</b>
<b>P920047</b>	EPT	SVT	462	OPC	Yes	Yes
<b>P930029</b>	Medtronic	SVT	683	OPC	Yes	Yes
<b>P950005</b>	Biosense	SVT	177	OPC	Yes	Yes
<b>P960016</b>	St. Jude	SVT	329	OPC	Yes	Yes
<b>P980003</b>	Cardiac Pathways	VT	188	RCT	Yes	Yes
<b>P990025</b>	Biosense	SVT	320	OPC	Yes	Yes
<b>P000020</b>	Bard	SVT	251	OPC	Yes	Yes
<b>P010068</b>	Biosense	Atrial flutter	198	OPC	Yes	Yes
<b>P020025</b>	Boston Scientific	Atrial flutter	250	OPC	Yes	Yes
<b>P020045</b>	CryoCath	SVT	166	OPC	Yes	Yes
<b>P030031</b>	Biosense	Atrial flutter	198	OPC	Yes	Yes
<b>P040014</b>	Irvine	SVT	165	OPC	Yes	Yes
<b>P040042</b>	Irvine	Atrial flutter	150	OPC	Yes	Yes
<b>P060019</b>	Irvine	Atrial flutter	326	RCT	Yes	Yes
<b>P020039/A6</b>	Cardima	AF	88	Patient as own control	Yes, but data unavailable	No

## Study Results Comparison

	MAE rate point estimate	MAE rate 95% CI upper bound	Acute success point estimate [95% LB]	Chronic success
<b>P920047 EPT</b>	3.1 (16/513)	4.6	93.0 (425/457)	83.4 [80.0] (397/476)
<b>P930029 Medtronic</b> <a href="http://www.fda.gov/cdrh/pdf/p930029.pdf">http://www.fda.gov/cdrh/pdf/p930029.pdf</a>	2 (11/683)		84	93
<b>P950005 Biosense</b> <a href="http://www.fda.gov/cdrh/pdf/p950005.pdf">http://www.fda.gov/cdrh/pdf/p950005.pdf</a>	2 (8/421)		96 [92] (164/171)	93
<b>P960016 St. Jude</b> <a href="http://www.fda.gov/cdrh/pdf/P960016b.pdf">http://www.fda.gov/cdrh/pdf/P960016b.pdf</a>	1.3 (4/318)	3.2	93.0 [89] (286/308)	82 [77] (150/195)
<b>P980003 Cardiac Pathways</b> <a href="http://www.fda.gov/cdrh/pdf/P980003b.pdf">http://www.fda.gov/cdrh/pdf/P980003b.pdf</a>	10.7 (16/150)	16.7	75 [68] (109/145)	55 [43] (41/75)
<b>P990025 Biosense</b> <a href="http://www.fda.gov/cdrh/pdf/P990025b.pdf">http://www.fda.gov/cdrh/pdf/P990025b.pdf</a>	2.5 (7/281)	5.3	97.1 [94.4] (269/277)	95.0 [90.3] (151/159)
<b>P000020 Bard</b> <a href="http://www.fda.gov/cdrh/pdf/P000020b.pdf">http://www.fda.gov/cdrh/pdf/P000020b.pdf</a>	4.4 (11/251)		93 [89] (230/247)	97 [95] (219/226)
<b>P010068 Biosense</b> <a href="http://www.fda.gov/cdrh/pdf2/P010068b.pdf">http://www.fda.gov/cdrh/pdf2/P010068b.pdf</a>	6.8 (13/191) 7.14 (13/182)	11.0 10.97	90.1 [87.2] (164/182)	94 (105/112)
<b>P020025 Boston Scientific</b> <a href="http://www.fda.gov/cdrh/pdf2/p020025b.pdf">http://www.fda.gov/cdrh/pdf2/p020025b.pdf</a>	8 (20/250)	10.8	94 [91.5] (235/250)	96 (146/152)
<b>P020045 CryoCath</b> <a href="http://www.fda.gov/cdrh/PDF2/p020045b.pdf">http://www.fda.gov/cdrh/PDF2/p020045b.pdf</a>	3 (3/103) AVNRT 8 (4/51) AVRT 8 (1/12) AF	8.5 combined	91[82] (94/103) 69 [51] (34/49) 67 [29] (8/12)	93 [85] 88 [69] 75 [28]
<b>P030031 Biosense</b> <a href="http://www.fda.gov/cdrh/pdf3/p030031b.pdf">http://www.fda.gov/cdrh/pdf3/p030031b.pdf</a>	15.8 (30/190)	21.0	85.3 [80] (162/190)	92.5 (136/147)
<b>P040014 Irvine Biomedical</b> <a href="http://www.fda.gov/cdrh/pdf4/P040014b.pdf">http://www.fda.gov/cdrh/pdf4/P040014b.pdf</a>	3.8 (6/158)	6.9	90.6 [86.1]	86.8 [81.5]
<b>P040042 Irvine Biomedical</b> <a href="http://www.fda.gov/cdrh/PDF4/p040042b.pdf">http://www.fda.gov/cdrh/PDF4/p040042b.pdf</a>	11.2 (17/152)	16.0	93.3 (140/150)	97.8 (137/140)
<b>P060019 Irvine Biomedical</b>	7 (12/174)		92.5 (161/174)	89 (144/161)
<b>P020039 Cardima</b>	6.9 (9/131)	13.0	?	~35.7 [25.6]