

FDA CASE STUDY

→ A stent company seeks to market a novel medical device

BRINGING AN INNOVATIVE DEVICE TO MARKET: PREMARKET APPROVAL (PMA) OF MEDICAL DEVICES

THIS FICTIONALIZED CASE STUDY IS THE THIRD IN AN EDUCATIONAL
SERIES PUBLISHED BY THE U.S. FOOD AND DRUG ADMINISTRATION.

THREE PEOPLE, ONE DREAM

Two years ago, Dr. Art Sartgen, a heart surgeon well-known for inventing and developing cardiovascular devices, and Dr. Flex Mater, a biomedical engineer specializing in materials science, founded a start-up company called ABC Stent Systems, Inc. (ABC). Together, they designed the Novel Bare Metal Coronary Stenting System (NBMCSS). An inventor with many patents, Dr. Mater had created a special alloy material that he and his partner believed would outperform existing stents in flexibility and shape retention, thereby reducing incidences of thrombosis (blood clotting) and restenosis (narrowing of the affected artery) in patients after stent implantation.

ABC recently hired a Regulatory Manager, Dr. Mary Laws, who has worked for 10 years in the **medical device** industry. Throughout her career, she has helped innovators of biomedical products market

their inventions with minimal delay by adhering to the U.S. Food and Drug Administration's (FDA) Application Integrity Policy, which helps assure companies maintain ethical standards and provide sound scientific data when applying for premarket approval of a medical device. For this venture, Dr. Laws' major responsibility will be to help get the NBMCSS to market by guiding ABC through the FDA regulatory process defined in the **Federal Food, Drug, and Cosmetic Act (FD&C Act)**.

A MEETING OF THE MINDS

The three executives of ABC convened in their new conference room to discuss the business side of their venture.

"There's a huge need for coronary stents here in the United States" Dr. Sartgen began. "In 2009, nearly 800,000 Americans died of cardiovascular diseases. In conjunction with medication, treatment options to reopen heart vessels damaged by coronary heart

disease include coronary artery bypass grafting, balloon angioplasty, or stent implantation. The coronary stent market was estimated to be over \$6 billion in 2010.

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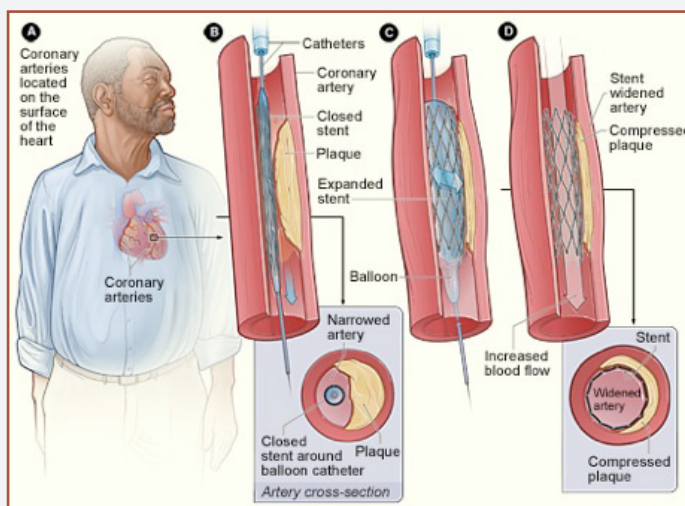
"Ideally, a stent procedure will improve blood flow to diseased heart muscles, reviving their normal function. However," Dr. Sartgen continued, "today's coronary stents have some serious limitations. There's a 10 to 40 percent incidence of restenosis within 6 to 12 months after a stent is implanted, and about 1 to 2 percent of stent patients develop thrombosis at the stent site, which can cause a heart attack, stroke, or other serious problems."

"And that's where we come in," Dr. Mater interjected. "Our early lab experiments have shown that the NBMCSS addresses those issues through its superior material characteristics, which allow the stent to sustain repeating or pulsating stresses. It can also reduce restenosis and thrombosis. I think this innovative device can make us a major part of that billion-dollar market!"

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STENT PROCEDURE

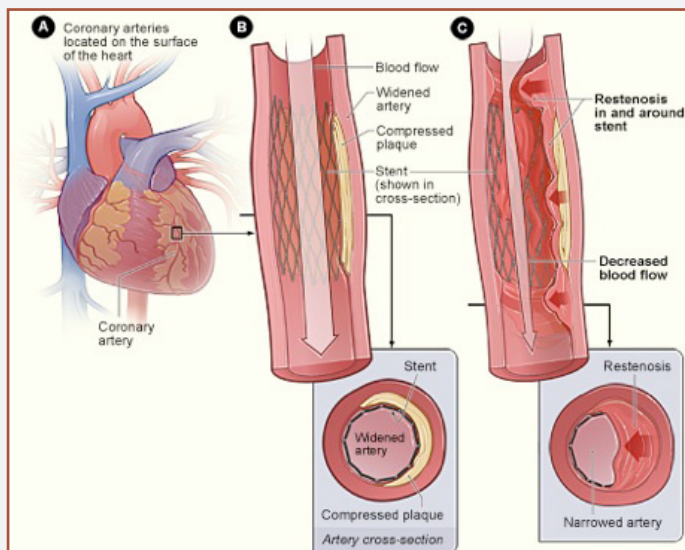
In an angiogram procedure, a cardiologist injects a special dye inside the patient's arteries to determine where they are narrowed or blocked by cholesterol-containing deposits (plaque). A stent is placed in the event that a blockage is identified in a vessel. The interventional cardiologist will then move a stent delivery system using a guide catheter to the lesion and inflate the balloon where the implantable stent is mounted. As the balloon inflates, it pushes the plaque against the artery wall and deploys the stent, widening the artery and helping restore blood flow. The implantable stent remains in the artery to keep it open. The balloon is deflated and pulled out along with the guide catheter. Over time, cells in the artery grow to cover the struts of the stent.



Legend:

- (A) The location of the heart and coronary arteries.
- (B) Deflated balloon catheter and closed stent inserted into the narrowed coronary artery. Inset image: cross-section of the artery with the inserted balloon catheter and closed stent.
- (C) The balloon is inflated, expanding the stent and compressing the plaque against the artery wall.
- (D) Stent-widened artery. Inset image: cross-section of the compressed plaque and stent-widened artery.

RESTENOSIS OF A STENT-WIDENED CORONARY ARTERY



Legend:

- (A) Coronary arteries located on the surface of the heart.
- (B) Stent-widened artery with normal blood flow. Inset image: cross-section of the stent-widened artery.
- (C) Tissue growing through and around the stent over time. This causes a partial blockage of the artery and abnormal blood flow. This process is called restenosis. Inset image: cross-section of the tissue growth around the stent.

Source: National Heart, Lung, and Blood Institute. (2013). "What Are the Risks of Coronary Angioplasty?" Explore Coronary Angioplasty. Available at: <http://www.nhlbi.nih.gov/health/health-topics/topics/angioplasty/risks.html>

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"You're right to be excited, Flex," said Dr. Laws. "If this device has the properties you think it does, the NBMCSS could be a major breakthrough in medical care. But remember, all you've got right now is preliminary information. Before we can market the stent, we'll have to scientifically demonstrate to the FDA that it's safe, effective, and performs as we're all hoping it will."

"Absolutely," Dr. Sartgen nodded. "It would be disastrous to cut any corners in the development of what could be a historical life-saving device. Mary, what will we need to submit to FDA to get the NBMCSS to market?"

"I'm happy to hear that Art," Dr. Laws smiled. Activating the projector screen at the end of the conference room table, she quickly pulled up a presentation entitled "FDA Premarket Approval of Class III Medical Devices."

"I'm going to give you a roadmap that will take us through the process of getting FDA approval," Dr. Laws continued. "But as I walk you through the details, I want you to keep in mind that the underlying purpose of these requirements is threefold: to ensure that our stent

"Class III devices support or sustain human life, are of substantial importance in preventing impairment of human health, or, can present a potential, unreasonable risk of illness or injury when used."

works as intended, fulfills the claims we're making for it, and doesn't subject patients to undue risk."

DR. LAWS' ROAD MAP

Major Milestones Before Marketing: Pre-Submissions, IDE, and PMA Applications

"To determine the appropriate regulatory pathway for a product," Dr. Laws explained, "the first thing you'll need to know is how FDA classifies your device. Before our meeting, I visited the FDA Web site and checked the Center for Devices and Radiological Health (CDRH) Product Classification database. The NBMCSS is a coronary stent (product code MAF), which is considered a Class III device."

"What are Class III devices?" asked Dr. Mater.

"FDA has created three regulatory classes for medical devices: Class I, II, and III. The assigned **classification** is based on the level of controls (regulations) necessary to assure the safety and effectiveness of the device. Regulatory control increases from Class I to III. Class III devices support or sustain human life, are of substantial importance in preventing impairment of human health, or, can present a potential, unreasonable risk of illness or injury when used."

"I see," said Dr. Matter. "So, the NBMCSS is a Class III device because

it is a cardiovascular **implant**: a high risk device that will support or sustain a patient who has restricted coronary vessels, but permanent implantation includes the risks of heart attack or even death."

"Additionally," said Dr. Laws. "Due to the level of risk, all Class III devices are subject to general controls and require a **Premarket Approval (PMA)** application (Title 21 CFR Part 814). However, there are two steps we'll need to take before submitting the PMA application: one highly suggested, and one required."

"First, I strongly recommend that we reach out to the FDA for preliminary guidance through a 'Pre-Submission.' FDA encourages manufacturers (**sponsors**), to ask for early guidance through meetings, e-mails, or telephone calls. This way, we can get the FDA's advice on the nonclinical testing proposal and clinical protocol design required for the next step in our PMA process: the Investigational Device Exemption (IDE) application (Title 21 CFR Part 812). I'll explain Pre-Submissions, PMAs, and IDEs more as we go along, but I wanted to familiarize you with the terms."

"This is starting to sound very complicated," Dr. Mater sighed.

Dr. Laws chuckled. "Don't worry, Flex; I've done this a few times. And let me reassure you, it will not only improve our stent, but will

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help us stay true to the business philosophy we created for ABC Stent Systems:

- Become the best-in-class among our competitors.
- Create products that save and improve the quality of human life.
- Design, manufacture, and market products as if intended for our loved ones.
- Adhere to all national and international rules and regulations that govern what we do.”

“I’m sold,” said Dr. Mater. “Take us through the steps we’ll need to obtain a PMA for our miracle stent.”

Steps to Obtain Premarket Approval

“In a nutshell,” said Dr. Laws, “our PMA application must submit valid scientific evidence proving the safety and effectiveness of our stent (21 CFR Part 860.7). Our PMA will include the final design concepts for the NBMCSS and our strategy for how we have tested and evaluated the device. Testing will occur in three phases:

- Nonclinical studies of **in vitro** bench testing
- Nonclinical studies of **in vivo** animal testing
- **Clinical investigations** of human subjects

Quality System Regulation (QSR)/Current Good Manufacturing Practices (CGMP): These are production and testing practices that help ensure safe, effective, and quality products. Our PMA submission should include a complete description of the design controls and **manufacturing information** our firm has on record to comply with the **Quality System Regulation** (21 CFR Part 820) for medical devices. FDA cannot complete a premarket review without this information, and its omission can delay the review process and marketing of the device. (See Exhibit 1)

Good Laboratory Practices (GLP): GLP are a set of principles that provide a framework within which laboratory studies are planned, performed, monitored, recorded, reported, and archived. FDA’s approach is based on requiring nonclinical facilities/laboratories to follow a GLP quality system to help ensure the integrity of data in nonclinical studies. A GLP system uses a risk-based approach, and in our case, should include nonclinical engineering tests of our stent. (See Exhibit 2)

Good Clinical Practices (GCP): FDA GCP regulations provide a framework for designing, conducting, recording, and reporting data from clinical trials involving human subjects. FDA GCP regulations include:

- 21 CFR Part 11 – Electronic Records and Signatures
- 21 CFR Part 50 – Protection of Human Subjects
- 21 CFR Part 54 – Financial Disclosure
- 21 CFR Part 56 – Institutional Review Boards
- 21 CFR Part 812 – Investigational Device Exemptions
- 21 CFR Part 814 – Premarket Approval of Medical Devices

Following the GCP regulations when we begin our clinical investigations will help assure that the rights, safety, and wellbeing of the people enrolled in our studies are protected. (See Exhibit 3)

We’ll submit the data we gather in the nonclinical testing steps in our IDE application. The IDE is what will allow us to test the stent in human subjects, the last phase of testing needed before we submit our PMA.”

Data Integrity and Best Practices

While planning our testing and evaluation strategy and going

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through the steps needed to complete our PMA, we should follow basic regulatory standards. It's vital that the FDA knows our data were generated using the best scientific practices, that our results are presented clearly and honestly, and that we haven't cut any corners. To achieve that, we'll follow published FDA guidance in three areas: **Current Good Manufacturing Practices (CGMP)**, **Good Laboratory Practices (GLP)**, and **Good Clinical Practices (GCP)**. These practices lay out the FDA's expectations for the kind of data quality and integrity they'll want to see in our applications. By demonstrating that we've adhered to these guidelines, we'll bolster FDA's confidence in our findings and increase the chance that our PMA will be accepted.

Pre-Submission

Laws pulled up the next slide in her presentation. "Now, before we begin nonclinical engineering testing, we'll need to detail the materials (generic chemical compositions and formulations) that make up our stenting system, as well as how the NBMCSS is constructed (the stent and its delivery system parts). We'll also provide documentation certifying that all incoming raw materials conform to specifications.

Once we've gathered this information in addition to any data we had previously, we should start putting together our Pre-Submission. A Pre-Submission is a formal written request for feedback

EXAMPLES OF SHELF LIFE TESTS ON STENT AND DELIVERY SYSTEM MATERIALS

Delivery System Dimensional and Functional Attributes

Dimensional Verification
Delivery, Deployment, and Retraction
Balloon Rated Burst Pressure
Balloon Fatigue
Balloon Compliance
Balloon Inflation and Deflation Time
Catheter Bond Strength
Tip Pull Test
Flexibility and Kink Test
Torque Strength
Coating Integrity
Stent Securement for Unsheathed Stents

Stent Dimensional and Functional Attributes

Dimensional Verification
Foreshortening
Radial Outward Forces
Particulate Evaluation

Purpose: Effects of aging on the materials of construction.

Note: For illustration purposes only. For details, please refer to FDA Guidance (2010) Nonclinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems, and FDA Guidance (2013) Select Updates for Nonclinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems. Draft guidances are subject to change and are not for implementation.

from FDA in writing or, if we choose, a meeting or teleconference. While it is not required, it is highly recommended, particularly in our case since our stent contains novel, never-before-seen technology that will make it a "first-of-its-kind" device. We can ask FDA for guidance throughout our testing stages. Doing so will not only familiarize the agency with our stenting system and its ongoing development, it may expedite our PMA process and improve our chances of getting the NBMCSS to market as quickly as possible."

In Vitro Nonclinical Testing

Once we've received feedback from FDA, Flex and his team can begin in vitro nonclinical engineering tests on the final design of our stent and its delivery system. These tests will ensure that the NBMCSS meets our **design specifications and controls**, and provide us with reasonable assurance that our device will pose no harm to humans when we start clinical trials in patients. We'll want to follow Current Good Manufacturing Practices (CGMP)

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throughout this stage of testing. The stent and its delivery system must meet all the predetermined acceptance criteria on all the test attributes (i.e., bench testing) developed as part of the risk analysis. For example, our device must be dimensionally correct, structurally fit, mechanically durable, and perform satisfactorily in its **intended use** environment. Flex’s team can create these in vitro bench test methods or use FDA-recognized consensus standards (See Exhibits 4 and 5).

To demonstrate that our stent doesn’t cause any harmful or unwanted effects when in contact with a patient’s circulating blood, we’ll conduct biocompatibility tests (See Exhibit 6). These tests may include the use of appropriate in vitro cellular or in vivo animal models to evaluate the possibilities of cell damage, gene mutation, and other adverse effects to patients. We can find additional guidance and standards for the design of these tests on the Product Classification page of the FDA Web site.

In Vivo Nonclinical Testing

The next round of nonclinical studies will use animal testing to give us a preliminary understanding of our device’s risks and provide information about local and systemic responses beyond what we can achieve from an in vitro study. In vivo testing will help justify the first human studies we undertake.

One of our first steps will be to choose an appropriate animal model that closest simulates conditions

in the human body for testing the stent. In vivo test data will demonstrate to FDA that our stent is sufficiently safe to be used for early human experiments. Animal testing is costly and can take months to perform, so we should ask FDA for guidance on our proposed animal study protocol models and testing protocols in our ongoing Pre-Submission process before we begin.

We must identify and evaluate the potential risks posed by the device using information from literature reviews, our competitors, FDA’s post-market databases, and our own in vitro testing (See decision tree on page 7). We’ll also want to make sure we follow Good Laboratory Practices (GLP) once we’ve decided our protocols.

Preparing for a Clinical Investigation: The IDE

When we’re satisfied with the nonclinical testing and we’ve collected all the necessary data, we’ll almost be ready to conduct the clinical investigations needed to prove that the NBMCSS is safe and effective when implanted in humans. Our next step will be to apply to the FDA for an Investigational Device Exemption (IDE), which will allow the stent to be used in a clinical study with human participants in the United States.

As part of our IDE application, we’ll have to comply with the Report of Prior Investigation requirement (21 CFR Part 812.27). This is where we report on those in vitro and in vivo

nonclinical tests Flex’s team will have performed to demonstrate to FDA that our stent will function as intended in bench testing and in the animal model. This data will give the FDA assurance of the safety, sterility, and biocompatibility of our stent, as well as present risk mitigation strategies for potential catastrophic failures like stent fractures.

The First in Human (FIH) study and the Institutional Review Board (IRB)

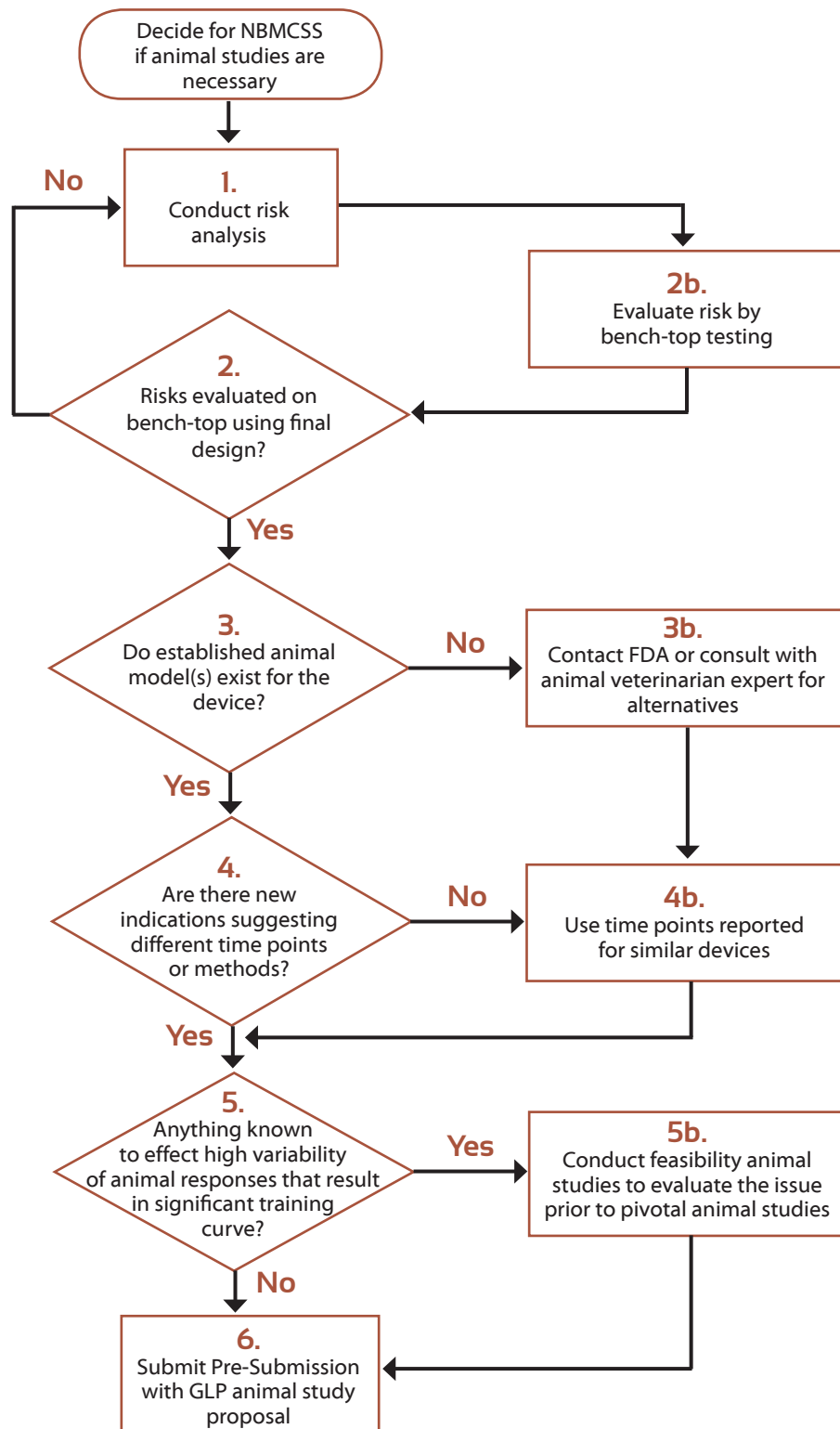
Because the NBMCSS is unique in many ways, we don’t have previous safety and effectiveness experience to rely on for clinical testing. We should sponsor an early feasibility study under a **First in Human Study** Investigational Device Exemption (FIH IDE) application. This type of IDE focuses on insights rather than data to support further IDE studies and the eventual PMA.

Since our stent is so novel, we’ll need to protect the people enrolled in our study as detailed in the Protection of Human Subjects regulation (Title 21 CFR Part 50) and identify and work with an established **Institutional Review Board (IRB)** (Title 21 CFR Part 56). An IRB is a committee of experts a company can formally designate to review, approve the initiation of, and conduct periodic review of their clinical investigations. We’ll submit our investigational plan and a report of prior investigations to the IRB, which will decide whether our stent

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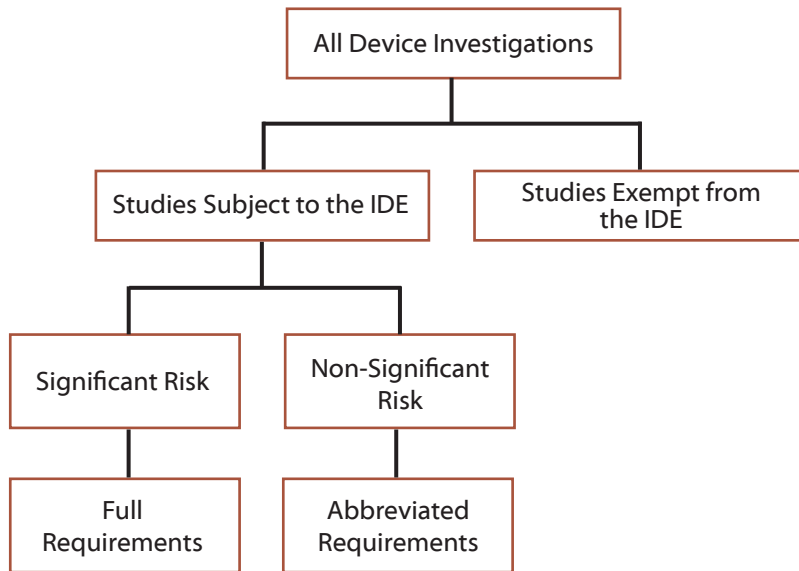
DECISION TREE FOR ANIMAL STUDIES IN NBMCSS



Note: For details please refer to the FDA Guidance (2010) General Considerations for Animal Studies for Cardiovascular Appendix B, pages 26–27.

BRINGING AN INNOVATIVE DEVICE TO MARKET: PREMARKET APPROVAL (PMA) OF MEDICAL DEVICES CONTINUED

DETERMINING SIGNIFICANT AND NON-SIGNIFICANT RISKS PRIOR TO IDE APPLICATION



Source: U.S. Food and Drug Administration. "What is an Investigational Device Exemption (IDE)?" Available at: <http://www.fda.gov/downloads/Training/CDRHLearn/UCM293098.pdf>

is a **significant or non-significant risk device** (See Exhibit 7). Remember, the NBMCSS is a Class III device, so the board will find that implanting an investigational stent is a significant risk and we'll have to prepare to fulfill all IDE requirements for conducting a study in the United States (See risk determination figure above).

Our clinical investigations will have to be approved by both the FDA and the IRB before we begin. As the sponsor of the investigation, we are responsible for complying with many elements of the IDE regulation, including labeling, distribution, informed consent, prohibitions, records, and reports (See Exhibit 8). We'll monitor the investigation and initiate frequent reviews by the IRB to

gain information on potential risks to protect the participants. We may also consider creating a Data Monitoring Committee to keep track of the ongoing validity and scientific merit of the trial. However, this is not required by FDA for every trial except in the case of waived informed consent (21 CFR Part 50.24). Monitoring procedures and other oversight of the clinical investigations are required (21 CFR Part 812.25[e]).

Informed Consent

To provide basic protection for our clinical trial participants, we will adhere to the requirements described in the regulation on **Informed Consent** of Human Subjects for an early feasibility study (21 CFR Part 50.25). This

means that we must explain the purpose of our study to participants, making it clear that we're doing a small study because there's not enough nonclinical data to support a larger investigation, and make participants aware of potential unforeseeable risks. We should be conservative when presenting the possible immediate and future benefits of using the device. The information in the consent form should not lead the participants to overestimate their chance of personal benefit. This approach is ethically correct, and the regulations require it.

Accommodating Change: The IDE Supplement

After we obtain clinical information from our first human studies, our subsequent clinical evaluations will depend on the stability of our stent's design, the availability of adequate data to justify the next study, and the purpose of that clinical study. As we learn more about the stent, we may want to make changes in the design to increase its safety and effectiveness. If we're going to use a modified device in a subsequent clinical study, we must submit an IDE Supplement to the FDA documenting the changes that were made. Once the IDE Supplement is approved, we may enroll additional participants in the early feasibility study.

If the design of our stent is near-final or final, and the results of the early feasibility study support

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appropriate for us to pursue either a **traditional feasibility study** (a clinical investigation used to gather preliminary safety and effectiveness information on a near-final or final device design to plan an appropriate pivotal study) or a **pivotal study** (a clinical investigation designed to collect definitive evidence of the safety and effectiveness of a device for a specified intended use). At that point, it will be very important to communicate with the FDA in an additional round of Pre-Submission guidance to help determine the most appropriate study to pursue.

The PMA Submission

At this point, we've completed in vitro and in vivo bench testing of our stent, we have an approved IDE, we've conducted clinical studies and analyzed the results per the protocol, we have followed CGMP, and we're now ready to submit our PMA. As we'll be supplying FDA with a large amount of data, it will be important to organize it in a logical, coherent way. FDA has published a guidance document we can follow on Acceptance and Filing Reviews for PMAs (Acceptance and Filing Reviews for PMAs, pages 19-21).

Tying Up the Loose Ends

Just a few more things to touch on before we reach the end of our roadmap: in our PMA application, we must include the proposed labeling for our stent (per our sponsor responsibilities) and we should understand that the FDA may require us to do additional "post-approval studies" after the stent is marketed. Once our stent

is marketed, we'll need to report any adverse events to the FDA (Medical Device Reporting [MDR]) and conduct voluntary recalls when necessary (21 CFR Part 803). We also need to follow FDA's requirements for registering and listing our firm.

THE WRAP-UP

"Any questions?" asked Dr. Laws. Pausing to take a much needed sip of water, she noted that her colleagues looked a bit shell-shocked. Dr. Sartgen was the first to respond.

"To be honest with you, Mary," said Dr. Sartgen, "All those requirements in the roadmap are making my head spin."

Dr. Mater spoke up. "And yet they make sense. At the most fundamental level, we present the FDA with scientific data that demonstrate that our stent is safe and that it works as we say it will. They evaluate what we give them and decide whether or not the device can be marketed."

Dr. Sartgen nodded, "Right. Okay, let me see if I can remember the sequence. We start with in vitro, nonclinical bench testing, and then proceed to in vivo tests using animals. We submit that data along with a proposed clinical trial design in our application for an Investigational Device Exemption, or IDE, which will enable us to test the device in humans for the pivotal study. And since our device is so unique, we'll use a First in Human IDE application. To oversee the

ethical dimensions of our human studies and ensure informed consent, we'll locate and work with an established Institutional Review Board. If we have to make changes in the device as our studies proceed, we'll inform the FDA using an IDE Supplement. And finally, we'll submit our Premarket Approval application, or PMA, using overall guidance supplied by the FDA. How's that, Mary? Do I have the basics under my belt?"

"Nice job, Art" said Dr. Laws. "But remember, our roadmap just skimmed the surface. We'll need more information as we go through this process, and our best source is the FDA itself. We should start communicating with them formally through a **Pre-Submission** as soon as possible so we can be sure we understand their expectations. We don't want to fail to generate the information FDA needs to establish the safety and effectiveness of the NBMCSS or do a lot of work that's not relevant to what the agency needs. Let's get started on the right foot."

"I'm still feeling a bit overwhelmed, but I'm also excited," replied Dr. Sartgen.

"As you should be," Dr. Mater smiled. "We've got a great product here that's going to be a real breakthrough in treating cardiac patients, and it's going to put this company on the map. Now we've got to go out and prove it. Let's get to work!"

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→ EXHIBITS

EXHIBIT 1. QUALITY SYSTEM INFORMATION FOR PREMARKET APPLICATION—CFR REFERENCES

Design Control Information

21 CFR Part	Activities
820.30(a)	Design Controls, General
820.30(b)	Design and Development Planning
820.30(c)	Design Input
820.30(d)	Design Output
820.30(e)	Design Review
820.30(f)	Design Verification
820.30(g)	Design Validation
820.30(h)	Design Transfer
820.30(i)	Design Changes
820.30(j)	Design History File

Manufacturing Information

21 CFR Part	Activities
820.20(e)	Quality System Procedures
820.50	Production Flow, Use of Standards
820.70	Purchasing Controls
820.72	Production and Process Controls
820.75	Inspection, Measuring, and Test Equipment
820.75(a)	Process Validation—Master Plan
820.80(b)	Process Validation—Procedure(s)
820.80(d)	Receiving Acceptance Activities
820.90	Final Acceptance Activities
820.100	Nonconforming Products
820.198	Corrective and Preventive Action
820.200	Complaint Files
820.200	Servicing

Notes: Design control and manufacturing information are key parts of a Premarket submission. This table shows examples of those requirements. For details, please refer to FDA Guidance (2003) Quality System Information for Certain Premarket Application Reviews.

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EXHIBIT 2. GOOD LABORATORY PRACTICES—CFR REFERENCES (21 CFR PART 58)

Selected Section	Area	Description
Subpart B. 29 – .35	Organization and Personnel	Qualification, experience, training, sanitation, and health precautions and independency of quality assurance unit from the study unit to assure the integrity of the conduct and results of the study
Subpart C. 41 – .51	Facility	Proper design to prevent adverse effect on the study
Subpart D. 61 – .63	Equipment	Design, maintenance, calibration
Subpart E. 29 – .35	Testing Facilities Operation	Standard operating procedures, consumables, and animal care
Subpart F. 105 – .113	Test and Control Articles	Characterization and handling of articles
Subpart G. 29 – .35	Protocol	Handling of contents, specimen, data, and their changes
Subpart J. 185 – .195	Records and Reports	Reporting contents, storage, retrieval, and retention of records and specimen
Subpart K. 200 – .219	Disqualification of Testing Facilities	Failure to comply with GLP requirements, communications, actions, and reinstatement

Note: GLP describes the required practices for sponsors to ensure data integrity and quality of animal studies. This table shows examples of GLP requirements.

EXHIBIT 3: ISO 14155:2011 CLINICAL INVESTIGATION OF MEDICAL DEVICES FOR HUMAN SUBJECTS – GOOD CLINICAL PRACTICES (GCP)

Section	Area	Description
1	Scope	Explains the purpose, principles, general requirements, and applicability of the standard
2	Normative Reference	References ISO 14971:2007
3	Terms and Definitions	Defines terminology involved in clinical practices
4	Ethical Considerations	Describes ethical principles and guidelines for the protection of human subjects of research based on the Declaration of Helsinki
5	Clinical Investigation Planning (CIP)	Describes clinical investigation activities, tasks, and responsibilities
6	Clinical Investigation Conduct	Describes how the CIP should be carried out
7	Suspension, Termination, and Close Out	Describes the roles, responsibilities, and procedures for the suspension, termination, and close out of a clinical investigation
8	Responsibilities of Sponsor	Describes the full responsibilities of the sponsor
9	Responsibilities of Principal Investigator	Describes the qualifications and responsibilities of the principal investigator

Note: GCP describes the required practices for sponsors to ensure the protection of human subjects. This table shows examples of good clinical practices requirements

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EXHIBIT 4. EXAMPLES OF NONCLINICAL ENGINEERING TESTS FOR THE STENT

Stent Dimensional and Functional Attributes	
Test/Activity	Purpose of Assessment
Dimensional verification	Proper size and accurate placement
Percent Surface Area	Biologic response of non-contact area
Foreshortening	Proper length selection and placement
Recoil for Balloon Expandable Stents	Proper device selection and long-term clinical outcome
Stent Integrity	Defects contributing to clinical complications
Radial Stiffness and Strength	Ability to resist collapse under loads
Radial Outward Forces	Effects of low or excessive radial forces
Mechanical Properties	Thermo-mechanical (temperature) effects on clinical performance
Stress/Strain Analysis	Device durability—loss of radial support, perforation of vessel by stent struts
Fatigue Analysis	Device durability—loss of radial support, perforation of vessel by stent struts, thrombus (blood clot) formation, focal restenosis
Accelerated Durability	Validation of fatigue analysis and evaluation of failure modes
Particulate Evaluation	Effects of embolic risk (blockage [e.g., clot, gas bubble] floating loose in a blood vessel) to patient
MRI Safety and Compatibility	Effects of movement, heating, image artifacts
Radiopacity	Assurance the stent will be visible in radiation imaging (e.g., x-ray)
In-Stent Restenosis	Effects on the interactions of stent

Notes: The purpose of these nonclinical engineering tests is to demonstrate that the functional and reliability performance of the stent fulfills specified requirements and intended uses. This table shows examples of such tests.

All tables in this guide were created for illustration purposes only. For details, please refer to FDA Guidance (2010) Nonclinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems and FDA Guidance (2013) Select Updates for Nonclinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems. Draft guidances are subject to change and are not for implementation.

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EXHIBIT 5. EXAMPLES OF NONCLINICAL ENGINEERING TESTS ON THE DELIVERY SYSTEM

Delivery System Dimensional and Functional Attributes

Test/Activity	Purpose of Assessment
Dimensional Verification	Abilities to track across lesions
Delivery, Deployment, and Retraction	Safe and reliable delivery of stent
Balloon Rated Burst Pressure	Survivability of balloon delivery system at specified burst pressure
Balloon Fatigue	Survivability of balloon delivery system at specified burst pressure after repeating specified number of cycles
Balloon Compliance	Correct size of stent to fit the target lesion
Balloon Inflation and Deflation Time	Acceptable occlusion time not to prolong ischemia and damage end organ
Catheter Bond Strength	Reliable catheter for delivery without vessel damage
Tip Pull Test	Reliable distal tip for delivery without failure and vessel damage
Flexibility and Kink Test	Ability to go through tortuous (twisting) vasculature without failure and vessel damage
Torque Strength	Ability to stand torsional (twisting) forces without failure and vessel damage
Coating Integrity	Ability of coating without delamination or degradation to impact clinical performance
Stent Securement for Unsheathed Stents	Inability of stent to dislodge from catheter within tortuous anatomy

Notes: These nonclinical engineering tests are performed to demonstrate that the functional and reliability performance of the stent delivery system fulfills specified requirements and intended uses. This table shows examples of such tests. For details, please refer to FDA Guidance (2010) Nonclinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems.

BRINGING AN INNOVATIVE DEVICE TO MARKET: PREMARKET APPROVAL (PMA) OF MEDICAL DEVICES CONTINUED

EXHIBIT 6. EXAMPLES OF BIOCOMPATIBILITY TESTS

Biologic Effect/Risk of Patient Coming into Contact with Materials	Test Purpose
Cytotoxicity	Cytotoxicity tests employing cell culture techniques used to determine the lysis of cells (cell death), the inhibition of cell growth, colony formation, and other effects on cells caused by the device, materials, and/or their extracts (see ISO 10993-5).
Acute systemic toxicity	Estimate the potential harmful effects of either single or multiple exposures during a period of less than 24 hours to medical devices, materials, and/or their extracts in an animal model (ISO 10993-11).
Genotoxicity	Test using mammalian or non-mammalian cell culture or other techniques used to determine gene mutations, changes in chromosome structure and number, and other DNA or gene toxicities caused by medical devices, materials, and/or their extracts. If any in vitro tests are positive, either in vivo mutagenicity tests shall be performed or it will be presumed that the material is mutagenic (see ISO 10993-3).

Notes: This battery of biocompatibility tests are performed to demonstrate that the stent system posed no unacceptable risks to humans through the use of animal models. This table shows examples of such tests. For details, please refer to FDA Guidance (2010) Nonclinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems, and ISO 10993 Biological Evaluation of Medical Devices.

EXHIBIT 7. FIRST IN HUMAN DEVICE EVALUATION STRATEGY

Device/Procedure Related Attribute	Potential Failure Modes	Potential Effects of Failure: Device	Potential Clinical Effects of Failure	Information Needed to Support Testing to Reduce Risk to Patient
Implant integrity	Structural failure of implant	Metallic fracture	<ul style="list-style-type: none"> ✓ Exacerbation of treated problem ✓ Foreign body embolization ✓ Trauma to adjacent structures 	<ul style="list-style-type: none"> ✓ Discussion of design concept to optimize integrity ✓ Comparison of design to marketed devices ✓ Strength testing ✓ Stress/strain analysis
	Corrosion	Metallic fracture	<ul style="list-style-type: none"> ✓ Exacerbation of treated problem ✓ Foreign body embolization ✓ Trauma to adjacent structures 	<ul style="list-style-type: none"> ✓ Comparison of materials to the sponsor's own marketed devices
Appropriate biological response	Loss of device function	None	<ul style="list-style-type: none"> ✓ Necrosis 	<ul style="list-style-type: none"> ✓ Comparison of design and materials to marketed devices ✓ Acute and medium-term implantation in an appropriate animal model

Notes: The goal of the FIH evaluation strategy is to explore and demonstrate that the stent system poses no unacceptable risks to humans. This table shows examples of some specific tests. For details, please refer to FDA Draft Guidance: IDE for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human Studies

BRINGING AN INNOVATIVE DEVICE TO MARKET: PREMARKET APPROVAL (PMA) OF MEDICAL DEVICES CONTINUED

EXHIBIT 8. RESPONSIBILITIES OF SPONSORS FOR SIGNIFICANT RISK DEVICE STUDIES

21 CFR Part	Area	Description
812.40	General	Select qualified investigators and provide them with the information needed to conduct the investigation properly. Ensure proper monitoring of the investigation and IRB review and approval, submit an IDE application to FDA for significant risk device studies, and inform the IRB and FDA promptly of any significant new information about the investigation.
812.42	FDA and IRB Approval	Cannot begin an investigation or any part of an investigation until an IRB and FDA have both approved the application or supplemental application.
812.43	Selecting Investigators	Select qualified, trained, experienced investigators to investigate the device.
812.43	Selecting Monitors	Select qualified, trained, experienced monitors to monitor the investigational study in accordance with the IDE and other applicable FDA regulations.
812.43	Device Control	Can ship investigational devices only to qualified investigators participating in the investigation.
812.43	Investigator Agreements	Must obtain a signed agreement from each participating investigator as required by the regulation.
812.45	Informing Investigators	Must supply all participating investigators with copies of the investigational plan and a report of prior investigations of the device.
812.46	Monitoring	Must secure investigator compliance, evaluate unanticipated adverse device effects, and follow up on subsequent actions as required. Must seek IRB and FDA approval for the resumption of terminated studies.
812.140	Sponsor Records	Must maintain accurate and complete investigation records.
812.150	Sponsor Reports	Must provide reports in a timely manner to FDA, the IRB, and/or investigators.
812.5	Labeling	An investigational device or its immediate package must bear a label with the prescribed information.
812.7	Promotion of Investigational Devices	A sponsor, investigator, or any person acting for or on behalf of a sponsor or investigator cannot promote, test market, commercialize, etc., investigational devices.

Note: Sponsors are responsible for all aspects of a Premarket submission. This table shows some major sponsor responsibilities in device studies.

BRINGING AN INNOVATIVE DEVICE TO MARKET: PREMARKET APPROVAL (PMA) OF MEDICAL DEVICES CONTINUED



GLOSSARY

Approval: Approval of a medical device must be obtained from the FDA by demonstrating that the device is reasonably safe and effective, and that the benefits outweigh the risks for the intended patient population before it can be put into commerce.

Approved Medical Devices: Approved medical devices are those devices for which FDA has approved a Premarket Approval (PMA) application prior to marketing. This approval process is generally reserved for high-risk medical devices and involves a more rigorous premarket review than the 510(k) pathway. <http://www.fda.gov/AboutFDA/Transparency/Basics/ucm194468.htm>

Clinical Investigation: A systematic investigation conducted to evaluate the safety and effectiveness of a medical device using human subjects or specimens.

Current Good Manufacturing Practices (cGMP): Production and testing practices that help ensure safe, effective, and quality products. In the United States, cGMP Regulations are promulgated by the FDA under the authority of the FD&C Act (Chapter IV for food; Chapter V, Subchapters A, B, C, D, and E, for drugs and devices). The “c” stands for “current”, reminding manufacturers that they must employ up-to-date technologies and systems to comply with the regulation. It is the manufacturers’ responsibility to be current.

Declaration of Helsinki: A set of ethical principles regarding human experimentation developed for the medical community by the World Medical Association (WMA). Widely regarded as the cornerstone document of human research ethics, it is not a legally binding instrument in international law, but instead draws its authority from the degree to which it has been codified in, or influenced, national or regional legislation and regulations.

Design Controls: Procedures established to control the design of a medical device in order to ensure that specified design requirements are met (21 CFR Part 820.30).

Device Classification: The FDA has established classifications for approximately 1,700 different generic types of devices and grouped them into 16 medical specialties referred to as panels. Each of these generic types of devices is assigned to one of three regulatory classes based on the level of control necessary to reasonably assure the safety and effectiveness of the device. The three classes and the requirements which apply to them are:

Device Class and Regulatory Controls:

1. Class I General Controls
 - With Exemptions
 - Without Exemptions
2. Class II General Controls and Special Controls
 - With Exemptions
 - Without Exemptions
3. Class III General Controls and Premarket Approval

Federal Food, Drug, and Cosmetic Act (FD&C Act): This is a set of laws passed by Congress in 1938 giving authority to the FDA to oversee the safety of food, drugs, and cosmetics. The Act has been amended many times, most recently to add requirements about bioterrorism preparations and user fees.

BRINGING AN INNOVATIVE DEVICE TO MARKET: PREMARKET APPROVAL (PMA) OF MEDICAL DEVICES CONTINUED

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First in Human (FIH) Study: A study in which a device for a specific indication is evaluated for the first time in human subjects. This case study only discusses FIH studies that meet the definition of an early feasibility study.

Good Clinical Practices (GCP): A set of guidelines that must be followed when conducting clinical trials to ensure that the rights and well-being of the trial participants are protected and that the data generated in the trial is valid. GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials involving human participants. The guidelines were developed in order to provide drug clinical trials with a unified standard across the European Union, Japan, and the United States and were labeled ICH-GCP at the International Conference on Harmonization (ICH), 1996. For medical devices, ISO 14155:2011 Clinical Investigation of Medical Devices for Human Subjects–Good Clinical Practice was developed and is the global standard for medical device GCP.

Good Laboratory Practices (GLP): A set of principles that provides a framework within which laboratory studies are planned, performed, monitored, recorded, reported, and archived. GLP helps assure regulatory authorities that the data submitted are a true reflection of the results obtained during the study and can therefore be relied upon when making risk/safety assessments.

Guidance Documents: Documents prepared for FDA staff, applicants/sponsors, and the public that describe the agency’s interpretation of or policy on a regulatory issue. They do not create or confer any rights for or on any person and do 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. Draft guidance documents are for the public to comment on and suggest changes for, but are not for implementation. (See 21 CFR Part 10.115 [b], [d], and [g])

Implant: A device placed into a surgically or naturally formed cavity of the human body intended to remain there for a period of 30 days or more. In order to protect public health, FDA may determine that devices placed in subjects for shorter periods are also implants.

In vitro: Outside the living body and in an artificial environment.

In vivo: In the living body of a plant or animal.

Indication for Use: The term “indications for use” describes the disease or condition the device will diagnose, treat, prevent, cure, or mitigate, including a description of the patient population for which the device is intended.

Informed Consent: A process by which a subject voluntarily confirms his or her willingness to participate in a particular investigation after having been informed of all aspects of the investigation relevant to the subject’s decision to participate. Documented by means of a written, signed, and dated informed consent form. Informed consent should include elements from 21 CFR Part 50.20.

Institutional Review Board (IRB): A board, committee, or group formally designated by an institution to review, approve the initiation of, and conduct periodic review of biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights, safety, and welfare of human subjects. The IRB should be established, operated, and function in conformance with regulation 21 CFR Part 56. The term has the same meaning as “institutional review committee” in Section 520(g) of the FD&C Act.

Intended Use/Purpose: Intended use means the general purpose of the device—or what the device does—and encompasses the indications for use. It is the use for which a product, process or service is intended according to the specifications, instructions, and information provided by the manufacturer.

BRINGING AN INNOVATIVE DEVICE TO MARKET: PREMARKET APPROVAL (PMA) OF MEDICAL DEVICES CONTINUED

Investigational Device: An unapproved new device or a currently marketed device being studied for an unapproved use in a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of the device.

Investigational Device Exemption (IDE): IDE refers to the regulations under 21 CFR Part 812. A regulatory submission to study a medical device in human subjects. IDEs are only required for studies performed in the United States. An IDE allows an investigational device to be used in a clinical study to collect the safety and effectiveness data required for a marketing application. An approved IDE means that the IRB (and FDA for significant risk devices) has approved a sponsor’s study application.

Investigator: An individual who conducts a clinical investigation, i.e., under whose immediate direction the investigational device is administered, dispensed to, or used involving a subject. In the event of an investigation being conducted by a team of individuals, “investigator” refers to the responsible leader of that team.

Manufacturing Information: Description of the methods used in, and the facilities and controls used for, the manufacture, processing, packing, storage, and where appropriate, installation of the device.

Medical Device: An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, "or accessory" that is the following:

- 1. Recognized in the official National Formulary, the United States Pharmacopeia, or any supplement to them
- 2. Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease in man or other animals
- 3. Intended to affect the structure or any function of the body of man or other animals

- 4. Does not achieve its primary intended purposes through chemical action within or on the body of a human or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes (Section 201[h] of the FD&C Act).

Monitor: (Noun) An individual designated by a sponsor or contract research organization to oversee the progress of an investigation. The monitor may be an employee of a sponsor, a consultant to the sponsor, or an employee of or consultant to a contract research organization. (Verb) To oversee an investigation.

Pivotal Study: A clinical investigation designed to collect definitive evidence of the safety and effectiveness of a device for a specified intended use, typically in a statistically justified number of subjects. It may or may not be preceded by an early and/or a traditional feasibility study.

Premarket Approval (PMA): The FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices. Any Premarket Approval application for a Class III medical device, including all information submitted with or incorporated by reference therein (21 CFR Part 814.3). Class III devices are those that cannot be classified as Class I or Class II devices because insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device, and either (1) are purported to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health; or (2) present a potential unreasonable risk of illness or injury.

Quality System Regulation (21 CFR Part 820): Requirements related to the methods used in, and the facilities and controls used for designing, manufacturing, packaging, labeling, storing, installing, and servicing of medical devices intended for human use.

BRINGING AN INNOVATIVE DEVICE TO MARKET: PREMARKET APPROVAL (PMA) OF MEDICAL DEVICES CONTINUED

Significant and Non-Significant Risk Devices: A “significant risk device” presents a potential for serious risk to the health, safety, or welfare of a subject. These devices are either intended as an implant or are substantially important in diagnosing, curing, mitigating, or treating disease (e.g., dental lasers, embolization devices for urological use, collagen, and bone replacements).

A “non-significant risk device” does not pose a significant risk to the human subjects (e.g., external monitors for insulin reactions, general biliary catheters, MRIs within specified parameters).

Sponsor: An individual, company, institution, or organization that takes responsibility for the initiation, management, and/or financing of a clinical investigation.

Traditional Feasibility Study: A clinical investigation commonly used to capture preliminary safety and effectiveness information on a near-final or final device design to adequately plan an appropriate pivotal study. As compared to an early feasibility study, more nonclinical (or prior clinical) data are necessary for approval to initiate a traditional feasibility study; however, a traditional feasibility study does not necessarily need to be preceded by an early feasibility study.



STUDENT ACTIVITIES

SESSION 1: BEFORE CLASS

I. Review the following materials:

Note: Draft guidances are subject to change and are not for implementation.

1. Dr. Michael Martinelli, Chief of Cardiology at St. Peter’s Hospital in Albany, NY, performs a cardiac catheterization via the femoral artery (Video: approximately 11 minutes)

Note: Contains images from a live surgery.

<http://www.youtube.com/watch?v=JeH4zPzQgRc>

2. Heart Health Stent Implantation Coronary Surgery, MedSelfEd, Inc.

(Video: approximately 8 minutes)

<http://www.youtube.com/watch?v=-pxRKkANOuI>

3. FDA Safety News: FDA-SHOW33-SEG1-AcculinkCarotidStent

(Video: approximately 2 minutes)

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/psn/transcript.cfm?show=33#1>

4. FDA Safety News: FDA-SHOW1-SEG3-CaptureDebris

(Video: approximately 1 minute)

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/psn/transcript.cfm?show=1#3>

5. Investigational Device Exemption Process (IDE) Video

(Video: approximately 11 minutes)

<http://fda.yorkcast.com/webcast/Viewer/?peid=46344ca5abbb465e88404a92eed542f71d>

6. IDEs for Early Feasibility Medical Device Clinical Studies, including Certain First in Human Studies (Mandatory)

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM279103.pdf>

7. FDA Decisions for IDE Clinical Investigations (Optional)

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM279107.pdf>

BRINGING AN INNOVATIVE DEVICE TO MARKET: PREMARKET APPROVAL (PMA) OF MEDICAL DEVICES CONTINUED

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8. Guidance on IDE Policies and Procedures (Optional)

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080203.pdf>

9. Information on Premarket Approval (PMA) (Optional)

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/default.htm>

II. Answer the following questions—Fundamental concepts:

1. Describe the intended use of the Novel Bare Metal Coronary Stent System (NBMCSS).

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073945.pdf>

2. How do you justify that the PMA application is the correct regulatory pathway for the NBMCSS?

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/default.htm>

III. Additional References

Note: Draft guidances are subject to change and are not for implementation.

1. Medical Devices: How to Market Your Device

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/default.htm>

2. The Federal Food, Drug, and Cosmetic (FD&C) Act

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/default.htm>

3. Subchapter II—Definitions § 321 (Page 32, Paragraph h)

<http://www.gpo.gov/fdsys/pkg/USCODE-2010-title21/pdf/USCODE-2010-title21-chap9-subchapII-sec321.pdf>

SESSION 2

I. Review the following materials before class:

Note: Draft guidances are subject to change and are not for implementation.

1. 21 CFR Part 820: Quality System Regulation (CGMP)

(Video: approximately 105 minutes)

<http://fda.yorkcast.com/webcast/Viewer/?peid=d2d4823b14a4e4ca6d60eae43c5ac9c>

2. Nonclinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems (Mandatory)

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM071986.pdf>

3. Select Updates for Nonclinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems (Mandatory)

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm366624.htm>

4. Quality System Information for Certain Premarket Application Reviews (Optional)

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070899.pdf>

5. ISO 14155:2011 Clinical Investigation of Medical Devices for Human Subjects—Good Clinical Practice (Optional)

<https://www.iso.org/obp/ui/#iso:std:iso:14155:ed-2:v1:en>

BRINGING AN INNOVATIVE DEVICE TO MARKET: PREMARKET APPROVAL (PMA) OF MEDICAL DEVICES CONTINUED

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6. ICH E6 Good Clinical Practice: Consolidated Guidance (Optional)

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073122.pdf>

3. FDA Good Laboratory Practices

<http://www.fda.gov/downloads/ICECI/EnforcementActions/BioresearchMonitoring/UCM133765.pdf>

II. Questions for in-class discussion:

1. Discuss the following:
 - a. What design controls will ABC Stent Systems, Inc., need to address in their PMA?
 - b. What manufacturing information will need to be addressed in the PMA for the NBMCSS?
2. What have you learned about the following aspects of GCP?
 - a. Human subject protection
 - b. Roles and responsibilities of those involved in clinical investigations
3. Discuss the types of nonclinical testing or studies that should be addressed for the NBMCSS:
 - a. Nonclinical engineering tests
 - b. Nonclinical in vivo tests

III. References:

Note: Draft guidances are subject to change and are not for implementation.

1. 21 CFR Part 58—Good Laboratory Practices
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=58&showFR=1>
2. 21 CFR Part 820 Preamble—Quality System Regulation
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/QualitySystemsRegulations/>

SESSION 3: AFTER CLASS


TEAM PROJECT AND PRESENTATION

I. Review the following materials:

Note: Draft guidances are subject to change and are not for implementation.

1. Acceptance and Filing Reviews for Premarket Approval Applications
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM313368.pdf>
2. Medtronic Endeavor Panel Meeting, October 10, 2007 (Reference provided for the educational purpose of illustrating a panel meeting discussion. The panel described in this case study only discusses bare stents, not drug eluting stents.)
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfAdvisory/details.cfm?mtg=686>
3. Abbott XIENCE V Meeting, November 29, 2007
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfAdvisory/details.cfm?mtg=687>

II. After reviewing the materials above, choose one of the options below for your team project:

1. Prepare an overall device evaluation strategy for the NBMCSS.
 **Hint:** Review IDE for Early Feasibility Medical Device Clinical Studies, including Certain First in Human Studies
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM279103.pdf>

BRINGING AN INNOVATIVE DEVICE TO MARKET: PREMARKET APPROVAL (PMA) OF MEDICAL DEVICES CONTINUED

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2. Create a nonclinical laboratory studies plan for the NBMCSS.

➤ **Hint:** Review Nonclinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM071986.pdf>

3. Create a clinical investigation plan for the NBMCSS.

➤ **Hint:** Review ISO 14155:2011 Clinical Investigation of Medical Devices for Human Subjects—Good Clinical Practice

<https://www.iso.org/obp/ui/#iso:std:iso:14155:ed-2:v1:en>

III. References:

Note: Draft guidances are subject to change and are not for implementation.

1. FDA Decisions for Investigational Device Exemption (IDE) Clinical Investigation

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM279107.pdf>

2. Information on Premarket Approval (PMA)

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/default.htm>