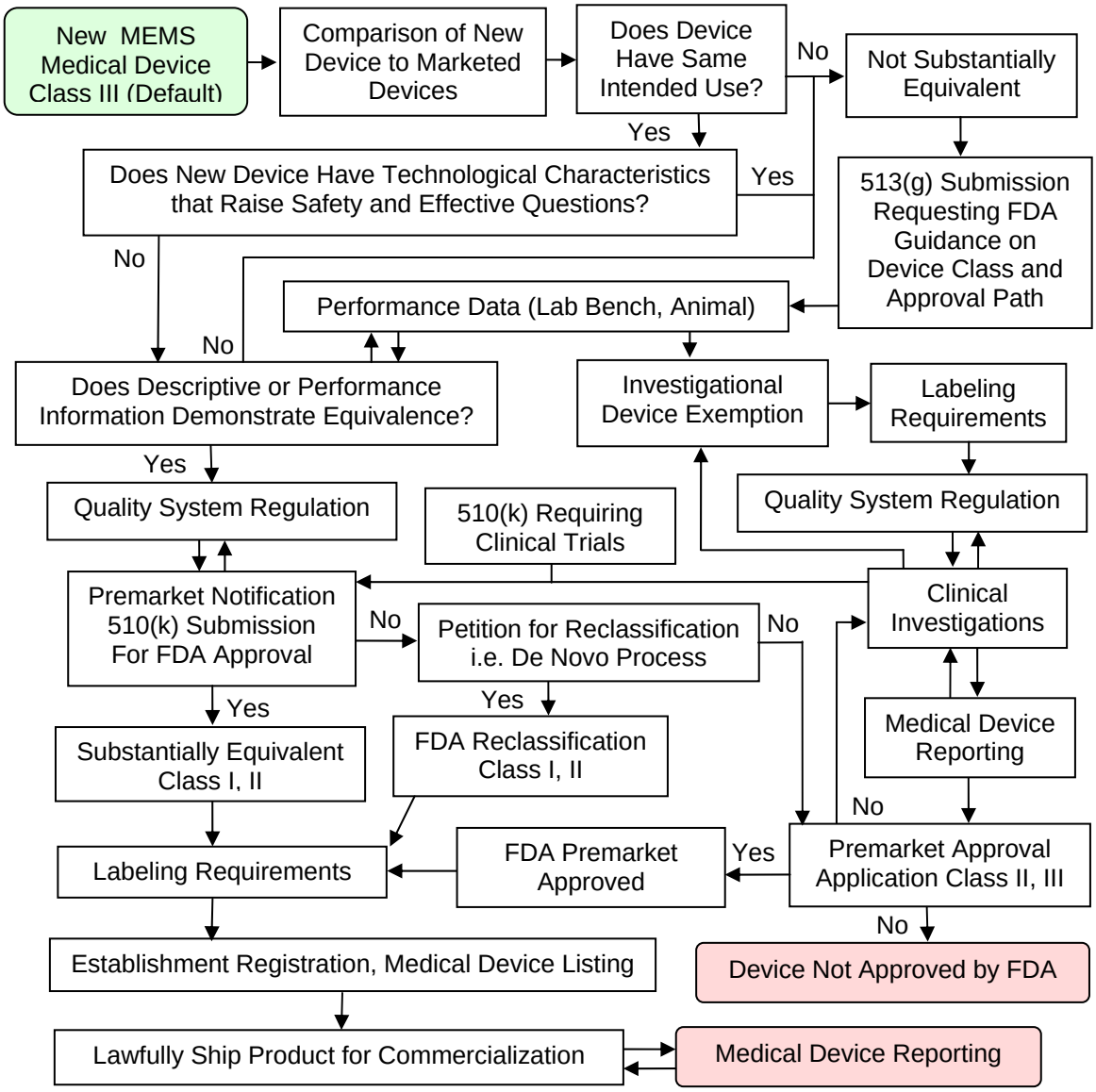
Navigating the Medical Device FDA Approval Process, *David DiPaola, 13 November 2012*

Introduction

With major advances in MEMS and nanotechnology and their proliferation into medicine, it is important to have a working knowledge of the critical steps in obtaining U.S. Food and Drug Administration (FDA) approval for commercialization. An understanding of the core elements and expedited review opportunities for medical devices provides entrepreneurs a key advantage in decision making, development and commercialization for the shortest time to market.

Many MEMS products intended for use with humans are considered medical devices under the FDA approval process. This includes products for diagnostics, monitoring, surgical and therapeutic applications. For a manufacturer to market or commercially distribute a medical device, it must first comply with the regulatory requirements of the FDA. The critical steps of this process are outlined in the flow chart below.

Flow Chart Overview of Critical FDA Approval Steps



Medical Device Classification I, II

Medical device class guidance is an important first step in this process as it defines the stringency and length of time for approval. The Federal Food, Drug, and Cosmetic Act (FD&C Act) establishes three classes of devices (I, II and III) based on risk and the regulatory controls needed to provide reasonable assurance of their safety and effectiveness. A class I device does not present a potential for unreasonable risk of illness or injury, is not for supporting or sustaining human life and is not of substantial importance in preventing impairment of human health. In addition, it is required that general controls be implemented prior to and maintained during commercialization. General controls include provisions to protect the consumer by eliminating unsafe, misbranded or poor quality devices, ensuring companies and devices are listed for reference, establishing an approval process to ensure safety, banning risky or deceptive devices, providing methods for repair, replacement or refund, maintaining information and history with proper documentation, restricting use of certain devices and ensuring good manufacturing practices. An example of a class I medical device using MEMS technology is air conduction hearing aides. MEMS microphones and speakers are used in hearing aids to pick up sound from the environment prior to amplification and play back the sound respectively. Its interesting to note that when wireless technology is added to these air conduction hearing aids, their classification moves from class I to class II.

Class II devices have moderate risk and hence require special controls in addition to general controls. The special controls are used to provide reasonable assurance of the safety and effectiveness of the device when sufficient information exists of their effectiveness. Class II special controls can include public performance standards, post market surveillance, patient registries, development and dissemination of guidelines, submission of clinical data in premarket notification, recommendations, and other appropriate actions as deemed necessary by the FDA. A class II device may be used for supporting or sustaining human life. An example of a class II FDA approved device is the ISSYS Micro-Coriolis Mass Flow Meter that uses proprietary resonant microtubes that will vibrate accurately to determine mass flow. Blood pressure monitoring is another example of a class II medical device that uses a MEMS piezo-resistive pressure sensor to monitor blood pressure (Spaeth 2010) and a MEMS accelerometer to sense arm position for obtaining a more accurate reading (Bonnema 2003).

Class III and PMA

The most stringent and highest risk classification are class III devices. Class III devices require premarket approval (PMA) to provide reasonable assurance of their safety and effectiveness because general and special controls alone cannot provide this assurance given existing information. In addition, the devices are intended for use in support or sustaining human life, of substantial importance in preventing impairment of human health or present potential unreasonable risk of illness or injury. The PMA application is a scientific, regulatory document that includes safety and effectiveness data from non-clinical laboratory studies and clinical investigations. Prior to marketing or commercializing a device, the applicant must receive FDA approval of the PMA application and have general and special controls in place. PMA can be a lengthy process requiring multiple years from concept to commercialization and millions of dollars in development costs.

Examples of class III devices using MEMS accelerometers are pacemakers and implantable cardioverter defibrillators (ICD) to monitor heart activity. St. Jude Medical more recently is using two dual-axis MEMS accelerometers that sense body position and movement in combination with other complex algorithms, data and equipment to provide protection from sudden cardiac arrest through lower tier and higher tier (shock) anti-arrhythmia therapy in ICD devices (Kroll 2007). Another notable MEMS based product currently in the PMA process is Senseonics' Continuous Glucose Monitoring System. The implantable device measures the fluorescent change in a glucose indicating polymer on its external surface. An embedded LED is used to excite the

polymer and its fluorescence change with changing glucose concentration of surrounding tissue is monitored (Senseonics 2012).

Official Classification and Expediting the Process

There are methods to streamline this process by getting the FDA involved early in the process, qualifying for expedited review (unmet medical need for life threatening or debilitating conditions) and, in future years, using the Innovative Pathway. Any new device intended for human use is automatically classified as class III. However, there are exceptions to this rule. Specifically, a new device can receive a class I or II designation if it is the same type as or substantially equivalent to an existing device in that respective class. In order for a new device to be officially classified by the FDA, the manufacturer must submit a premarket notification or 510(k). Prior to filing a 510(k), a 513(g) Request for Information can be filed with the FDA requesting their opinion on the class of the generic type that the new device falls into, whether 510(k), PMA or neither are required for the generic type and other applicable requirements for approval. Upon receipt of the 513(g), the FDA shall provide the requester a written response within 60 days. Successful use of this petition process to lower classification is extremely valuable to reduce stringency of the approval process hence expediting time to market.

An example of an existing class II MEMS device where reclassification was successful is an implantable intra-aneurysm pressure measurement system. In October 2005, CardioMEMS EndoSensor AAA Wireless Pressure Measurement System obtained a class II designation for their MEMS pressure sensor that monitored intrasac pressure during endovascular abdominal aortic aneurysm repair. The device could also be used as an adjunctive tool in the detection of intraoperative endoleaks. Initially, this device was designated class III because it was introduced post amendments with no predicate. Later in this article, the process for reclassification of this device from class III to II will be discussed in more detail.

It is cautioned that a difference in technological characteristics between a new and lawfully marketed predicate device can prevent a substantially equivalent approval unless the manufacturer can demonstrate equivalence regarding safety and effectiveness. For example, the ISSYS Micro-Coriolis Mass Flow Meter was determined to be substantially equivalent to a non MEMS electric monitor for gravity flow infusion system. However, this may not always be the case especially if a new MEMS technology is not as safe as an existing approved technology and hence poses additional risk.

510(k) and Exemptions

In order for a MEMS manufacturer to market or commercially distribute a device intended for human use, they must submit a 510(k) unless it is exempt (rare for MEMS products), it meets certain guidelines or PMA is required. A large portion of class II devices require a 510(k). Exemptions include preamendment devices, those for humanitarian purposes, devices of minimal risk, custom not for sale devices and devices that are repackaged or distributed by a third party. More specifically, a 510(k) is required when first introducing a device for marketing or commercial distribution post-amendments, you propose a different intended use for a device in commercial distribution or there is a change or modification of a device that could significantly affect its safety or effectiveness. The purpose of the 510(k) is to demonstrate to the FDA that the device to be marketed is as safe and effective as or substantially equivalent to an existing device. There are a number of class I (almost all) and II devices exempt from premarket notification. A comprehensive list of exempt devices and exemption guidelines are provided on the FDA website.

An example of a class II exempt device is the BodyMedia Fit. This particular system uses a MEMS 3-axis accelerometer to monitor motion and steps taken and combines it with information obtained from other sensors to monitor calorie burn. The Argus II Retina Prosthesis System from Second Sight is also exempt under the Humanitarian Device Exemption (HDE). The Argus II is for people who have retinitis pigmentosa, a form of inherited blindness. It has a MEMS electrode array that

emits small pulses of electricity to stimulate the retina's remaining cells based on information from a video camera. These cells then transmit the visual information to the optic nerve in the brain to help patients interpret visual patterns of light. This helps in the recognition of doors and sidewalks and allows people to become more independent (Second Sight 2012). HDE is intended for products that affect less than 4000 individuals per year in the US and R&D payback may not be obtained. Requirements for safety are similar to PMA but the product's effectiveness at its intended purpose is not required to be shown. Specific class I and II devices that are not exempt, may be eligible for third party review in place of the FDA saving time and maybe cost.

510(k) Approval and Reclassification

If the 510(k) is approved, the FDA will provide a letter declaring the device substantially equivalent and it can be marketed and commercialized in the US. In cases where substantially equivalent is not found, the applicant may submit another 510(k) with new, more convincing data of equivalency, request class I or II designation through the De Novo process, a risk-based classification specific to a particular device when no predicate exists, or submit a PMA application. There is also the option to file a reclassification petition with required supporting data and reasoning to request the FDA to move a device including all substantially equivalent devices of a generic type to a lower, less stringent class. Product development protocol (PDP) is another time saving method used when PMA applies. The PDP is an agreement between the applicant and the FDA that defines design details, development activities, outputs, acceptance criteria and milestones upfront before clinical evaluation begins. This information is then communicated between parties as it becomes available to expedite the approval process.

The De Novo process was used to reclassify the CardioMEMS EndoSensor AAA Wireless Pressure Measurement System from class III to class II. In this risk based classification, the FDA concluded that special controls in addition to general controls provided reasonable assurance of the safety and effectiveness of this type of device. This was the initial classification of this device under the generic name Implantable Intra-aneurysm Pressure Measurement System because no predicate existed. The ruling also applied to substantially equivalent devices of this generic group. All subsequent CardioMEMS EndoSure products such as for thoracic aortic aneurysms were determined substantially equivalent to this initial product classification.

Investigational Device Exemption and Clinical Trials

In support of a 510(k) or PMA application, premarket clinical trials may be required. To begin clinical studies, an investigational device exemption (IDE) is required prior to the start of the study unless the device is exempt such as one solely used in research with laboratory animals. The approved IDE allows the investigational device to be used to collect safety and effectiveness data in humans. Most PMA applications require clinical studies while only a small percentage of 510(k) have this requirement.

Clinical studies with devices are divided into two groups by the FDA: those with significant risk and those with nonsignificant risk. In the case of significant risk, both institutional review board (IRB) and FDA approval are required. For nonsignificant risk cases, only IRB approval is needed before the study can begin. Additional requirements for clinical evaluations include the sponsor obtaining informed consent from all patients, having proper labeling stating investigational use only, monitoring of the study and maintaining proper records and reports.

Once the IDE is approved, the device can be shipped for clinical investigations without complying with other requirements of the FD&C Act. While the clinical study is conducted, specific regulations and requirements (Good Clinical Practices or GCP) must be adhered to. Guidance for Good Clinical Practices are well documented on the FDA website. MEMS manufactures do not need to submit a 510(k), PMA, list their device or register their company while the device is under investigation.

Listing, Quality System and Medical Device Reporting

Additional documentation filings required in the FDA approval process include listing the devices manufactured by a business including activities performed on those devices at the facility and registration of the company with the FDA. In addition, applicants must establish and follow a quality system (QS) also known as current good manufacturing practices and provide proper labeling on both investigational and commercialized products.

Furthermore, the sponsors are responsible for Medical Device Reporting (MDR). With MDR, user facilities submit reports on device-related deaths to the FDA and the device manufacturer and device-related serious injuries to the manufacturer or FDA if the manufacturer is not known. A summary of all reports must be submitted to the FDA on an annual basis. Manufacturers must report deaths, serious injury and malfunctions within 30 days to the FDA. In addition, the manufacturers must report events that require remedial action to prevent an unreasonable risk of substantial harm to the public health and other events required by the FDA. The FDA website provides clear guidelines on each of these topics.

Case Study

An excellent case study to highlight MEMS in the FDA approval process is the ingestible sensor manufactured by Proteus Digital Health. The ingestible sensor is a MEMS medical device that is used to monitor identity and timing of pill ingestion. The MEMS sensor consists of a 1 mm square silicon chip that contains trace amounts of copper and magnesium. When ingested, a small voltage is generated when it comes in contact with stomach fluid that can be detected on the skin's surface. The ingestion recorder or patch worn on the skin then wirelessly transmits the data to a computing device such as a mobile phone which collects and displays the ingestion data as well as your activity, heart rate and body position (Proteus Digital Health 2012, Maxmen 2012). This information can then be transmitted to loved ones or the person's physician for better point of care. Proteus began collaboration with the FDA in 2008, started clinical trials in 2009 and the ingestible sensor was approved in July 2012 for use with placebo pills (Proteus Digital Health 2012, Murry 2012). The sensor obtained a class II designation through the De Novo process as there was no predicate and thus found not substantially equivalent. This reclassification was completed by filing a 510(k) and a follow up petition. It did not receive expedited review and was not eligible for third party review (FDA 2012). The company now has approval to market and commercialize this system with placebo pills in the U.S. and is working to obtain approval to integrate the system directly into pharmaceutical drugs (Murry 2012).

Conclusion

The FDA approval process can be daunting with many pages of laws and guidance, required documents, controls, validation, analysis and complex exemptions. Once device classification, premarket notification, premarket approval and investigational device exemption are understood, many of the other items such as medical device reporting become easier to put in place. With MEMS devices poised to revolutionize medical devices with their technological sophistication and micro size, the next 10 years are primed to see major breakthroughs in how medicine is practiced.

The majority of the information communicated in this document was obtained from the Federal Food, Drug, and Cosmetic Act (FD&C Act) based on the United States Government Printing Office Federal Digital System (FDsys) version of the United States Code, 2006 Edition, Supplement 3. In addition, Medical Device Amendments enacted May 28, 1976, all additions and subtractions to the Amendments, the FDA's databases and the FDA's guidance documents provided on their website were used.

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Bio:

David DiPaola is Managing Director for DiPaola Consulting a company focused on engineering and management solutions for electromechanical systems, sensors and MEMS products. A 16 year veteran of the field, he has brought many products from concept to production in high volume with outstanding quality. His work in design and process development spans multiple industries including automotive, medical, commercial and consumer electronics. Previously he has held engineering management and technical staff positions at Texas Instruments and Sensata Technologies, authored numerous technical papers and holds 5 patents.