Development and Regulation of Cardiac Pacemakers

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Abstract

Pacemakers are medical devices whose primary purpose is to provide a pulse or pace when the heart is unable to do so intrinsically. They are indicated for a variety of medical conditions related to Bradycardia, or a slower than normal heart rate. Although these innovative devices offer effective therapy, they also raise regulatory concerns due to their complexity. This paper will discuss how such devices are presently developed and regulated in an evolving technological and regulatory environment.

AAMI – Association for the Advancement of Medical Instrumentation

FDA – Food and Drug Administration

IDE – Investigational Device Exemption

ISO – International Standards Organization

PMA – Premarket Approval

QSR – Quality System Regulations

TIR – Technical Inspection Report

Introduction

According to the American Heart Association statistics, there are about 3 million people worldwide who have pacemakers, and an additional 600,000 are implanted each year. Pacemakers are electro-mechanical devices, with a pulse generator module that interfaces with the heart by means of lead wires that are connected to heart tissue. While early devices were simple, providing only therapy for at rest slow heart rates, modern devices are software controlled and offer additional beneficial features such as rate responsiveness that enables pacing of the heart at faster rates during periods of increased cardiac demand. A recent example is the new **Ingenio** pacemaker product line from Boston Scientific, which announced FDA approval on May 7, 2012 (Comcast, 2012). The

PRNewswire quoted the President of the Heart Rhythm Society who said*: "Matching the patient's need to increase their heart rate with their precise activities is the main goal of cardiac pacing. Achieving that match depends on having the right tools such as an MV sensor and intelligent programming."* This particular pacemaker product line is also designed to work with a remote patient monitoring system that enables physicians to perform remote follow-ups via website access. Modern pacemakers, such as **Ingenio,** are very powerful, capable devices and rely on special controls to mitigate the risk associated with ever-increasing complexity.

Development – Regulations and Standards

Pacemakers are Class III medical devices, and as such must be designed within a quality system mandated by the FDA in 21 CFR part 820, known as QSR. One important component within the quality system that facilitates risk mitigation is Design Controls (see Table 1), specified in 21 CFR part 820.30. These controls include design and development planning, design input, design output, design review, design verification, design validation, design transfer, and design history. A practical example of how these controls work in practice can be demonstrated by the software process used in the above mentioned Boston Scientific **Ingenio** pacemaker. Although design controls are intended to be employed at a macro level, meaning the entire product, in actual practice many of these controls relate specifically to pacemaker software design. It's in this magic world that a general purpose computer is transformed into a special purpose computer that provides beneficial therapy.

Table 1 - Risk-based Classification, Level of Regulatory Control & Submission Type

510 (K) Exempt	Class I	Class II	Class III
Very Low	Low	Medium	High
General Control (may or may not be GMP exempt)	General Controls Premarket Notification or 510 (K)	General & Special Controls 510 (K) submission	General & Special Controls, Premarket Approval

Source: (Carey, 2010)

Like a physical product, software has lifecycles which are specified in the ISO 62304 standard. In this context, software development involves strategic planning and then ultimately the creation of requirements that are part of the design input. The design output is the implementation of the design also known as the software code. Per design controls, this implementation is subject to peer review and then ultimately tested. The downstream testing is where verification (confirmation that the output meets the input requirements) and validation (confirmation that the product meets user needs) occur. QSR validation includes a "risk analysis." Risk is defined as the "*combination of the probability of occurrence of harm and the severity of that harm*" (ISO, 2011). Hence, part of a pacemaker submission is a Hazard Analysis which is a document that identifies hazards, their severity, and mitigation strategies. Although the FDA produces guidance documents to help manufacturers better understand FDA expectations, in the area of risk assessment the FDA embraces and even defers to standards organizations as well as collaborative guidance produced by industry. Pacemaker development takes into consideration international standards such as ISO 14971, and Technical Inspection Reports such as TIR32 from AAMI. Moreover, throughout the entire pacemaker design and development process records are maintained that ultimately become part of the product's design history file.

However, developing software driven medical devices is challenging due to an evolving and ever-changing regulatory environment. This is summarized well by following statement: *"Medical device software is an area where the FDA regulatory framework remains unsettled"* (Kahan, 2009). This '*unsettled framework'* is a cause for concern, especially considering changes and delays in product approval process and requirements affect a manufacturer's ability to market a device according to a business plan. Thus, changes at the FDA have enormous economic and social consequences. Protecting the public health, while facilitating the development of innovative medical devices, is most certainly a delicate balancing act.

Governing Regulations

The FDA essentially provides three regulatory options for medical devices to qualify for commercial distribution:

1. 501(k) submission to demonstrate that a new device is as safe and effective as an already legally marked device
2. PMA or Premarket Approval submission to demonstrate that a device is safe and effective for its intended use as manufactured
3. HDE or Humanitarian Device Exemption application for use in small patient populations, typically less than 4,000 people

As Class III medical devices, pacemakers require compliance with the PMA process. For approval, they must follow 21 CFR part 814, guidance documents, and all other laws and regulations related to the development, testing, manufacturing, labeling, marketing, and distribution of medical devices. The Traditional PMA process typically requires a pivotal clinical trial which generally requires at least 1500 participants. The clinical trial process must also be compliant with IDE regulations as stated in 21 CFR part 812 when the trial

is conducted in the United States. Sometimes though, clinical studies may not meet their intended endpoints in which case they can be performed again. In studies involving medical devices such as pacemakers the failure to meet efficacy endpoints can, for example, be the result of the participant having access to better drugs. This may happen when the trial predicts a specified number of heart events that may not occur. Without such expected events, often mitigated by effective drugs, therapy is not delivered by the device, and hence endpoints are not met.

In other cases a new device may be able to leverage a pre-existing PMA and submit a supplemental PMA instead of a Traditional PMA. How are supplemental PMA's different and under what circumstances are they permitted? According to (Kahan, 2009), *"The best way to determine whether changes to the device are significant enough to require the submission of a new Traditional PMA is to assess the data required to support the changes."* In the case of the aforementioned **Ingenio** device, a supplemental PMA was used since an existing Traditional PMA for well-understood pacemaker therapy was applicable (Alsop Interview, 2012). For supplemental PMA's of this type, previous clinical data is relevant. For instance, although **Ingenio** requires additional clinical data, the trial or Ivory Study is limited in scope to only the new features available in certain device models (Clinical Trials.gov, 2012). This allows the **Ingenio** base models to be approved in parallel with the ongoing clinical trial. Moreover, the Ivory Study also reveals that an IDE may not be necessary for the PMA process since this particular study is being conducted outside of the United States. In these cases, per 21 CFR 814.15, the studies must be conducted according to the laws of the country hosting the trial or in

conformance to the Declaration of Helsinki in situations where it provides better protections for trial participants than do the laws of a particular country. Thus, conducting trials outside of the United States cannot be used as a means to circumvent the necessity the FDA places on the protection of clinical trial subjects.

Conclusions

In this brief examination of cardiac pacemakers, we focused on the core activities involved in their development within a highly regulated industry. By drawing on the experiences of the **Ingenio** pacemaker device, we discussed a practical use of FDA mandated design controls within the QSR framework, the relevance of guidance and international standards, highlighted the key components of the PMA process, and covered some of the pertinent rules related to clinical trials. Yet, this discussion does not end with market approval. Class III devices such as pacemakers must remain compliant after approval, and this includes post-market studies and surveillance. Additionally, issues discovered in fielded devices are tracked and monitored per many more regulations that require corrective and preventive measures to be taken when necessary. Based on the trends in recent years, pacemaker technology will no doubt progress as will the regulatory guidelines, which should lead to interesting and challenging careers in both engineering and regulatory affairs disciplines.

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