CHAPTER **36**

Framework for Understanding Medical Device Development

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INTRODUCTION

This article is a general description of medical device development, to help the reader understand how devices come to market. The map described gives a basic understanding to the practitioner who may want to investigate development and possible commercialization of a product. The process involves discovery and revisions of an idea, within the context of a marketable item that is commercially viable. In the medical space there is the added regulatory component that must be understood before commercialization.

DEVELOPING A MEDICAL DEVICE IN AN ENGINEERING FRAMEWORK

The first step in medical device development is identifying a need or problem, and substantiating that need with real-world scenarios. For example, a difficult surgical procedure to perform may be enhanced by use of a tool or instrument that has never before been created. Likewise, a new material may be developed that would be beneficial in the operative setting compared to existing materials. Once that need is established, a unique method of solving the problems introduced by that need is created. Examples would be a special distractor for small bone spaces, or a plate made from materials with improved resistance to fatigue failure. The inventor designs a solution that is elegant and functional, and satisfies the requirements of the identified problem.

Conceptually, this process is easy to understand. But fundamentally the process is quite complicated. Development of a prototype itself may be cumbersome unless the inventor has a workshop or access to a lab. This is why many novel creations are developed in university or other academic settings. Proper development usually will involve use of some computer methods, so an understanding of Computer-Aided Design (CAD) is important. Real world objects exist in 3-dimensional (3-D) form so advanced computer modeling using programs like Solidworks are then necessary to create a model that can be read by a 3-D printer, Computer Numerical control machine, or the like. Once a prototype is made, real-world problems with the design can be identified. Generally this is through bench or lab testing. Revisions are made in the digital world, new prototypes are made, bench tested, and repeated until a final design is established. At this point, more sophisticated testing is then performed, depending on the particular device and how predicate devices have been tested.

The methods of testing are established and published in American Society for Testing and Materials (ASTM) papers. For most professionally developed medical devices there is adherence to International Standards Organizations (ISO) specifications. For example, ISO 9001:2000 discusses the adoption of a process approach to development, and ISO 13485:2003 explicitly requires a process approach toward quality management for medical device manufacturing. Engineers know these specifications and follow the directives as part of a quality system. Quality System Requirement (QSR) is the Food and Drug Administration's (FDA) procedural version of these processes.

The FDA in the US has established protocols for device testing based on predicate devices, following the methods of ASTM, and these tests are generally repeated for duplicate or iterative devices. For example, a new staple will have to pass static, dynamic, and pull out tests using a particular amount of force through a particular number of cycles to establish equivalence to existing devices. Testing will reveal weaknesses in the device, and improvements to overcome these weaknesses go back to the CAD step, where a new design will emerge eventually that satisfies the functionality test and material tests.

DEVELOPING A MEDICAL DEVICE IN A REGULATORY FRAMEWORK

Premarket regulation of medical devices by the FDA is a relatively recent phenomenon. In 1976, Congress enacted Medical Device Amendments to the Federal Food, Drug and Cosmetic Act partly as a response to growing concerns over the safety and effectiveness of medical devices. The Amendments classified new devices as low (I), moderate (II), or high risk (III) (1). Medical technology regulated as devices in the US includes items as simple as latex gloves and as complex as magnetic resonance imaging (MRI) scanners and pacemakers. The Amendments gave the FDA oversight authority to regulate the clearance and approval of medical devices prior to marketing, as well as to enforce regulations on good manufacturing practices and post-market reporting requirements (2).

The first step in the acquisition of clinical data for high-risk (class III) medical devices is for industry to obtain approval from the FDA for initial clinical testing. Significant

risk devices include implants and life-supporting or life-sustaining devices that have the potential for serious risk to the health, safety, or welfare of a subject, or devices that are of substantial importance for diagnosing, curing, treating, or mitigating disease (e.g., devices intended to diagnose or treat human immunodeficiency virus). The more extensive regulatory requirements for significant risk devices often delay clinical testing, and because of this, many devices begin testing outside of the US. Class III devices are subject to the most stringent levels of evaluation through the Premarket Approval Application (PMA.) (Figure 1)

In the US, low risk (Class I) devices such as surgical gloves and hand-held instruments are subject to certain general regulatory controls, such as requirements for labelling, good manufacturing practices and registration of manufacturing facilities, and listing of devices with the FDA. Most are not required to undergo pre-market clearance through the 510(k) process (see below). The moderate risk posed by Class II devices such as orthopedic implants requires that the manufacturer comply with "special controls" in addition to the general controls required for Class I devices (1). For example, special controls may include adherence to performance standards, guidance documents, or implementation of postmarket surveillance measures, such as patient registries.

Pre-market applications for Class II devices may be initiated via a Premarket Notification 510(k), an FDA process based on the argument that the device is essentially equivalent to one that has already been approved by the FDA. This pathway to market does not usually require clinical data derived from randomized trials regarding the effectiveness of a device for a given use or population of patients (1,3-5). For the new device to be considered "substantially equivalent" to the predicate device, it has to be demonstrated to be similar in design and intended use. If any technological characteristics differ from the predicate, the manufacturer has to provide performance data to demonstrate that the changes do not raise new questions of safety and effectiveness, and that the new device is at least as safe and effective as the predicate device (6). Performance data may range from bench data to those from controlled clinical studies, depending on the issues raised by the new technological characteristics of the device. Only approximately 10-15% of Premarket Notification 510(k) applications contain clinical data derived from human studies (2).

Class I:

Pose the least amount of risk to consumers. General controls ensure the safety and effectiveness of devices once they are manufactured. General controls include:

- Good manufacturing practices (GMPs)
- Standards and Reporting Adverse Events to FDA
- Registration with FDA
- General record keeping requirements

Most Class I devices are exempt from pre-market submission. Examples include latex gloves and oxygen masks.

Class II:

Pose more risk to consumers than do Class I devices. Therefore, Class II devices are subject to "special controls" in addition to general controls.

Special controls include:

- Labeling requirements (information that must be included on a product label)
- Device specific mandatory performance standards
- Device specific testing requirements

Most Class II devices require pre-market notification by way of a PMA (if no predicate) or 510(k) if substantially equivalent to a legally marketed device already approved.

Class III:

Usually, Class III devices support or sustain life, are implanted in the body, or have the potential for unreasonable risk of illness or injury. Examples include pacemakers, breast implants, and HIV diagnostic tests. As a result, Class III devices require premarket approval. To receive this, a manufacturer must prove that a device is safe and effective. Class III devices are also subject to general controls.

Figure 1. Depending on the type of device the Food and Drug Admininistration has broad classifications based on the risk posed by a device. Medical devices can change classification systems depending on specific characteristic or modifications, or the results of scientific data.

Many 510(k) applications reviewed are for modifications to, or new features for commercially available devices. The PMA application contains non-clinical information pertaining to the design and characteristics of the device, and a section on clinical investigations that includes safety and effectiveness data. The type of data required for approval ranges from multi-center randomized clinical trials for the highest-risk devices to single site non-randomized cohort studies for devices deemed to be of lower risk. The FDA may call on an advisory panel consisting of expert clinicians and scientists to review the clinical evidence for a new device and give recommendations, although the agency is not bound by those recommendations.

One final pathway for approval is the Humanitarian Device Exemption (HDE) regulatory pathway that is available for devices that are intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 4,000 individuals in the US per year. An HDE application is similar in both form and content to a PMA, but is exempt from the effectiveness requirements of a PMA. The application however must contain sufficient information for the FDA to determine that the device does not pose a significant risk of illness or injury, and that the probable benefits outweigh the risk of injury or illness from the device's use. Additionally, the applicant must demonstrate that no comparable devices are available to treat or diagnose the disease or condition, and that the manufacturer could not otherwise bring the device to market.

As discussed above, in the process of development an inventor will identify some predicate device that his or her concept most closely resembles. This pathway will occur most often, unless the device meets Class III designation or there is no predicate device due to the device's novelty. In these cases, a more extensive application (PMA, Pre-Market Approval) will be required by the FDA that demonstrates "sufficient valid scientific evidence that provides reasonable assurance that the device is safe and effective for its intended use." Generally, for Class II devices, the FDA will want to see equivalence in safety and efficacy to an already approved item. For example, a novel bone screw has a myriad of similar products already approved in the market to demonstrate what testing is required.

Once enough information is established to demonstrate a device's safety and efficacy, a manufacturer can then apply to the FDA for permission to market the device to the public. This Premarket Notification, or "510k," indicates that the device is substantially similar to other devices on the market. Included in the application is the supporting test data comparing the device to other legally marketed devices (devices approved and in commercial distribution in the US before May, 28, 1976, or to a substantially equivalent device as determined by the FDA.) If the device receives approval from the FDA it can be legally marketed for its stated indications.

Just as bench testing can reveal weakness in a prototype, real world scenarios can reveal new safety concerns once the device is on the open market. Therefore the FDA will monitor device safety after approval. They do this through in-person manufacturer inspections, which are either routine or generated from a particular problem. Manufacturers are to self-report any problems identified as part of Good Manufacturing Practices.

DEVELOPING A MEDICAL DEVICE IN A LEGAL FRAMEWORK

Understanding the process of development within the framework of a heavily regulated and scrutinized industry would not be complete without a discussion of the legal ramifications. While reducing a concept to practice may be guided by the specifications outlined by the FDA, ultimately going to market depends a great deal on novelty. This is because so many devices are iterations of existing technology. For example, novelty in orthopedic screws is difficult to achieve given the market saturation. This brings up many fundamental questions, the most basic being why do we need so many devices that do the same thing?

Technological advances in metallurgy, machine processes, biocompatibility, and other parameters make iterations of implants worthy and accepted by the marketplace. More elegant solutions to existing devices also generate interest and ultimately market acceptance. Finally, competition is healthy in an environment where cost is always a concern and performance can never be good enough.

However, there is a substantial concern, given the myriad of devices arriving in the marketplace, of intellectual property infringement and protection for the inventor. Therefore, a critical step in determining marketability of a device is investigating prior art by way of a thorough patent search. Issued patents, both foreign and domestic, as well as published patent applications should be examined for identical or substantially similar claims to the newly invented device. Although databases exist through search engines like justia.com and patents.google.com, as well as on the US Patent and Trademark Office (USPTO) website (uspto.gov), a truly exhaustive search should be done by a patent attorney.

Once a patent search has been done and it appears that there is novelty, consideration should be given to filing a provisional patent. This establishes with the patent office a reduction to practice, i.e., an idea that has been brought into the real world and a declaration of when and by whom. A provisional patent is not a patent application that will be

reviewed by any patent issuing authority for merit or patent issuance, it is merely a broad description of the invention for the purposes of staking a claim in the event a full utility patent is filed.

The USPTO will grant patent if all three of the following are met: utility (the product is useful), novelty (it does not already exist or exist in another form), and inventive step (simple alteration or combinations of existing technology could not result in the new device.) Generally, novelty and inventive step are the most difficult to establish. For example, a claim for a new bone screw may demonstrate novelty in orthopedics, but research into general construction methods may reveal a substantially similar device and consequently the new device does not meet the novelty requirement. The inventive step is the most difficult parameter, as this is where true innovation lies, when something is produced that the world has never seen before.

The provisional patent gives the inventor one year to discover any revisions or new technology within the claims. Before the expiration of this time a full utility patent (and separate design patent, if this is appropriate) will need to be filed with the USPTO as well as any foreign entities where protection is desired. The patent examination process can take several years, although the inventor has the right to label items "patent pending" while this process is ongoing.

For the inventor who spends considerable time and energy on developing a new device, protection of the idea is very important and should be a part of the development process. In the course of engineering, the inventive step may actually exist in the manufacture of a device, or may only be able to be achieved given a certain method or steps to creation. This is why meticulous record keeping is essential and the entire process should be carefully guarded as intellectual property (IP.) The value of this IP can not be determined in advance and so an inventor should proceed as if there is infinite value in the know-how.

Many devices have been copied legally because of a failure to adequately protect the development sequence, including divulging integral concepts to other individuals without a non-disclosure agreement (NDA.) Therefore, in the course of prototyping, consulting, testing, and discussing marketing, every person should be bound by a NDA and records of these NDAs should be kept indefinitely. Without these in place, an entire body of work can essentially be worthless to the inventor. No patent can issue if the information is in the public domain prior to any claims.

In conclusion, medical device development follows a well-established path that involves simultaneous efforts in engineering, regulatory analysis and testing, and protection of intellectual property. Often these steps overlap each other as scientists invent, refine, and test the devices.

Many times, concepts are not practical. For example, there may be a limited market, the cost of manufacture exceeds what the market will bear, or the timing of device introduction is poor. But many times the market is ripe and the need is latent until just the right device comes along.

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