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Medical Device Development

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The development of a successful medical product requires not only engineering design efforts, but also clinical, regulatory, marketing and business expertise. This paper reviews items related to the process of designing medical devices. It discusses the steps required to take a medical product idea from concept, through development, verification and validation, regulatory approvals and market release.

Keywords — **Medical device, development, verification, validation, regulatory approvals, market release.**

I. INDUSTRY OVERVIEW

While in the last two decades economic cycles and uncertainties have affected several industries, the medical device sector reaped the benefits of earlier investments and delivered unmatched improvements in people's quality of life. As a result, between 1980 and 2000, the heart attack mortality decreased by about 40%, the stroke deaths declined by 37%, diabetes complications were 25% fewer and breast cancer mortality was 20% lower [1]. Americans now have a life expectancy at birth of 76.5 years. Those Americans who have reached their 65th birthday are likely to live another 16-19 years [2]. The industry fundamentals have been positively affected by favorable demographics and continued growth in health care expenditures. In the United States, the number of Medicare beneficiaries (people older than 65 years) is expected to rise from about 40 million, in 2000, to over 75 million, in 2030 [2]. As such, health care expenditures for hospital care, physician care, drugs, medical devices and medical nondurables have risen considerably in the last decade. In 2001, these expenses reached $1.42 trillion [3]. The rate of spending growth is expected to continue at an average annual rate of 6.9 percent into the next decade when health care expenditures will exceed $2.8 trillion and will represent 17% of GDP [2]. Such elevated levels of funding are particularly important for makers of high-tech medical device products and give the U.S. medical device industry an important competitive advantage. It comes with little surprise that the U.S. medical device manufactures lead the world both in terms of revenues and innovation. The U.S. medical technology industry is the largest producer of medical devices and diagnostics, with production evaluated at $77 billion in 2002 [4]. Further, the U.S. is one of the world's largest exporters of medical technology, selling to other countries an estimated $20.3 billion. Figure 1 indicates the industry distribution of revenues in major international markets [4]. Note that in 2000 the worldwide medical technology revenues were $169 billion. By comparison, in the same year the semiconductor industry dollar size reached about $150 billion [5]. In the U.S, most of the medical device companies participate in the cardiovascular sector (e.g. implantable pacemakers and defibrillators, stents, etc.) and are responsible for about 41% of the total U.S. market. Orthopedics companies (e.g. artificial joint and limb replacement devices) are second with a market share of 24% [6].

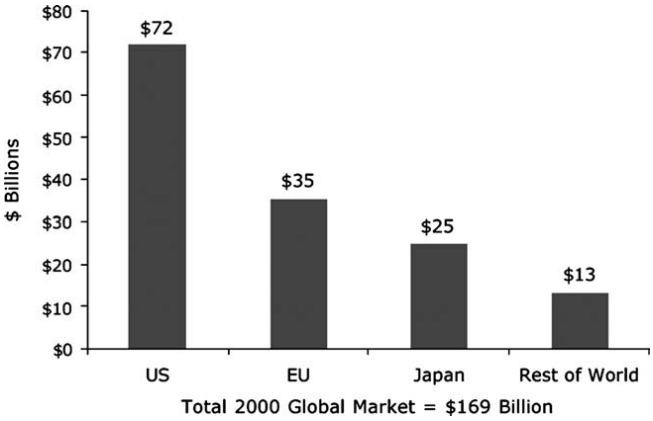

Fig. 1. International Markets for the Medical Device and Diagnostics Industry in 2000.

The other sectors, in decreasing market share order, are: urology – 12%, neurology – 9%, digestive disease – 8%, and peripheral vascular – 6%. As a sign that innovation is more likely to occur in small companies, in 2001 more than 80% of medical device firms had less than 50 employees [6]. The typical evolution of a company is to grow from a seed concept, to a single-product start-up stage then into a larger, more diversified organization. The seed concept, the idea that gives genesis to a company, comes from sources such as academia, entrepreneurial physicians or other individuals or small groups with enough medical and engineering background to have an in-depth understanding of the medical problem and to offer a realizable solution. The funding risk is, most of the time, assumed by venture capital firms, by organizations and foundations that offer grants, or by 'angel' groups (e.g. family members, close friends). Among government organizations that fund medical device research, the National Institute of Health (NIH) and National Science Foundation (NSF) offer most substantial grants. Corroborating the exponential growth in medical device innovation seen in the 90s, the NIH budget has grown from $6.5 billion in 1991 to $27.8 billion in 2004 [7]. Similarly, private funding by venture capital has almost quadrupled from $454 million in 1992 to $1.6 billion in 2003 [4]. Another aspect that underlines the innovation outburst and the fierce competition in the medical device industry is the intellectual property portfolio. Critical for the survival of both small and large companies and a direct measure of their investment in research and development, the number of medical device patents issued by the U.S. Patent Office has more than doubled, from 4178 in 1989 to 9091 in 2003 [4].

II. MEDICAL DEVICE DEVELOPMENT

The above background about the medical device industry is useful for understanding the steps needed to turn an idea into a medical product. As shown in Fig. 2, a typical development process is a traditional waterfall model. The design proceeds in a logical sequence of phases or stages. Requirements are developed, and a device is designed to meet those requirements [8]. The design is then evaluated, transferred to production, and the device is manufactured. In practice, feedback paths would be required between each phase of the process and previous phases, representing the iterative nature of product development. When the design input has been reviewed and the design input requirements are determined to be acceptable, an iterative process of translating those requirements into a device begins. The first step is the conversion of the requirements into system or high-level specifications. At this stage, these specifications represent a design output. Upon verification that the high-level specifications conform to the design input requirements, they become the design input for the next step in the design process, and so on. Design reviews are conducted at strategic points in the design process. For example, a review is conducted to assure that the design input requirements are adequate before they are converted into the design specifications. Design reviews also assure that the device design is adequate before prototypes are produced for simulated use testing and clinical evaluation. Similarly, a validation review should be conducted prior to transferring the design to production. Generally, design reviews are used to provide assurance that an activity or phase has been completed in an acceptable manner, and that the next activity or phase can begin. The FDA web site provides an useful analogy that clarifies some of these concepts [8]: "Fuel efficiency is a common design requirement. This requirement might be expressed as the number of miles-per-gallon of a particular grade of gasoline for a specified set of driving conditions. As the design of the car proceeds, the requirements, including the one for fuel efficiency, are converted into the many layers of system and subsystem specifications needed for design. As these various systems and subsystems are designed, design verification methods are used to establish conformance of each design to its own specifications. Because several specifications directly affect fuel efficiency, many of the verification activities help to provide confirmation that the overall design will meet the fuel efficiency requirement. This might include simulated road testing of prototypes or actual road testing. This is establishing by objective evidence that the design output conforms to the fuel efficiency requirement. However, these verification activities alone are not sufficient to validate the design. The design may be validated when a representative sample of users have driven production vehicles under a specified range of driving conditions and judged the fuel efficiency to be adequate. This is providing objective evidence that the particular requirement for a specific intended use can be consistently fulfilled."

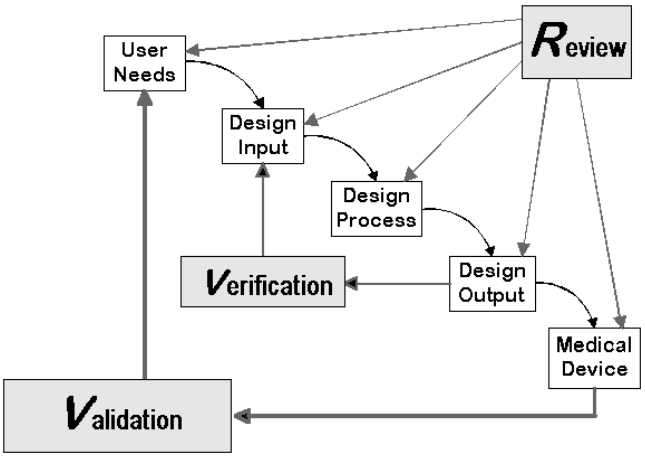

Fig. 2. Typical medical device development process flow [8].

In practice, the FDA guidance above is implanted by breaking up the development process in a few relevant phases. Although various companies or entities use different names for these phases, a common pattern can be established.

Funding Phase

Even for a great idea, to get its development off the ground, the right amount of funding must be secured. For start-ups, this phase involves identifying the right clinical need, understanding its market potential, understanding the intellectual property (IP) landscape (i.e. prior art patents and patent applications that will have to be filed to cover the idea), and anticipating the regulatory approval and reimbursement roadmap. Rough schedules, resources and budgets are drafted. With this package, funding is sought from applicable sources. In an established company, same elements are put together in a funding proposal that is submitted for Senior Management's approval.

Concept Phase

With funding found or approved, the team now focuses on producing the first version of specifications that describe the medical device, according to the original idea. Typically, a marketing specifications document is created that describes the high-level features of the product. A product requirements specification document is also produced that translates the marketing specifications in engineering terminology that can be used later on to produce documents such as hardware, software or mechanical design requirements specifications. In this phase, the grounds for risk analyses documents are set. The team produces a first version of a risk analysis that addresses potential risks related to the new product. Clinical risks, production risks, environmental risks, management risks, are all part of the items covered by this analysis. Based on the progress made in this phase, the project plan produced during the previous phase is updated. The regulatory, reimbursement and clinical roadmaps are reviewed and, if necessary, updated. Similarly, the IP

strategy is revised. Production plans are created and the marketing and sales outlooks are updated.

Development Phase

This phase is one of the most complex and critical phases of product development. The lower level requirements specifications documents are created in this phase. If applicable, hardware, software, mechanical requirements specifications are created and approved. Actual design/development commences. As per the FDA process flowchart above, verifications and reviews are necessary in order to ensure that the design complies with applicable requirements. To help with this part of the process, which in certain cases can be quite complex, traceability matrixes are generated. A traceability matrix maps requirements and known or potential risks to verification or validation steps that prove that respective requirements are met and respective risks addressed. If needed, in order to better gauge progress, engineering prototypes may be developed. All this progress must be formalized under document and revision control procedures. The 'freeze' of the preliminary design represents a major development milestone. This step can be achieved when the design is proven to have potential for meeting requirements and shown to comply with quality and regulatory controls. For example, certain key parameters of an algorithm can be set, or certain electronic component values can be fixed. A software program can now be compiled with the intention of initiating module and integration testing. Integrated circuits or printed circuit boards (PCB) can now be committed to a final engineering release. Of course, depending on complexity, additional revisions could still be made based on appropriate quality controls. This design freeze sets the stage for the next phase of the process, the Verification and Validation Phase. To close the Development Phase, the requirements specifications must be formally approved and the verification and validation (V&V) test protocols must be signed off. All other elements of the project plan (e.g. risk analyses, regulatory, reimbursement, clinical roadmaps, IP, production, marketing and sales strategies) must be updated.

Verification and Validation Phase

The design, completed in the previous phase, is tested to formally prove that it meets the requirements specified both by lower-level (e.g. hardware or software requirements) and by higher-level (e.g. product or marketing requirements) specification documents. Testing against requirements specifications is referred to as *verification*. Testing that proves compliance as per intended use is referred to as *validation*. Very few designs pass verification and validation from the very first attempt. A realistic project plan should allocate time, resources and funding for potential iterative steps of V&V. In compliance with quality controls and procedures, aspects of the design can be changed if found to not meet requirements. For example, minor bugs may be found in software, or minor routing errors may be detected on a PCB. In such cases, only incremental V&V steps are taken to prove that after such changes the design still meets requirements. Complete re-testing would only be required if major changes to the design have been performed. Appropriate revision controls should be employed to track changes and trace various versions of the design that ultimately result in the final product. Once V&V testing is completed, based on the defined regulatory and clinical roadmap, the product could now be submitted to agencies, such as the FDA, for either a full market approval or for a clinical trial approval. The regulatory approvals are territory dependent. In the US, the FDA approves the release of medical products to markets or for clinical trials. In Europe, agencies must obtain a CE mark prior to a market release. Other countries, such as Japan, Australia, Canada, etc., have their individual regulatory agencies that have to approve the product prior to its being market-released to the respective country. Some countries accept the approval from the FDA or the CE mark with minimal or no additional regulatory review. Products that have a lower level of risk, such as a medical grade thermometer, may receive applicable approval without a clinical trial. Products that involve greater degrees of risks, such as an implantable cardioverter defibrillator (ICD) may, typically, require clinical trial testing prior to approval for a full market release. These aspects of the regulatory and clinical roadmaps are addressed in the V&V phase. The project team should also prepare the project for entering the Production Phase. To close the V&V Phase, the V&V test reports must be signed off and all design documents must be released to production-level versions. All other elements of the project plan (e.g. risk analyses, regulatory, reimbursement, clinical roadmaps, IP, production, marketing and sales strategies) must be updated.

Production Phase

This phase may also be known as Scale-Up or Manufacturing Phase. The intent of this phase is to create appropriate processes and documentation that would ensure that the product is manufactured according to quality standards. Manufacturing procedures are developed to explicitly describe the steps required to produce the device. Tools that may be required for product manufacturing are also developed in this phase. In recent years, the FDA has put significant emphasis on the verification and validation of the manufacturing process. Whereas in the Development Phase the team proved that the design met requirements, this phase must document that production can be scaled up while design input requirements are still met. For example, tools that are used to measure certain features of the product must be calibrated and proven to adequately perform their intended job. Components received from outside vendors must pass through incoming inspection to document that they comply with required specifications. Operators and assemblers must receive appropriate training. A certain number of products may need to be manufactured in order to prove with statistical significance that the output of the production line meets design requirements. To be cost-effective, yield and re-work percentages must be

documented and verified that they meet business requirements. Of course, if the product meets design requirements but yields are too low then business competitive aspects of may be negatively impacted. Based on the product risk level, the FDA provides detailed guidelines regarding its expectations for manufacturing process V&V. Another important objective of this phase is to secure appropriate levels of inventory for either conducting approved clinical trials or for a full market release, as per the regulatory roadmap.

Market Release Phase

Not all territories may receive respective regulatory approvals at the same time. Therefore, the market penetration of the new product may be gradual. For devices that carry lower risk levels, it is typical to gain CE mark approval first. Such approval would allow the team to release their product to European markets first and draw a certain amount of revenues. These revenues, particularly for start-ups, could be very helpful in supporting continuation of the project or the development of subsequent products. If the product risk level is higher, to the point where clinical trials are needed to validate safety and efficacy, typical strategies would involve first seeking an investigational device exemption (IDE) from the FDA. Upon completion of the clinical study and after receiving FDA approval, the product could then be released to the US markets. Release to other countries may require separate approvals and separate clinical trials, depending on the product level of risk. A product release to the Japanese market would require approval from their Ministry of Health, Labor and Welfare and, if applicable, a separate clinical trial. The Market Release Phase also requires that a significant effort be spent on preparing training information for physicians and patients. Companies produce marketing materials, white papers and work with physicians on publications that spread the knowledge about optimal use of the product. Similarly, patient education can be equally important for certain products. It is also good practice and a regulatory requirement to monitor the quality of the product after release to markets. The project team should set up quality controls that monitor customer complaints and any field failures or malfunctions of the product. Corrective action mechanisms must be set in place so that any potential field quality concerns are addressed timely. The post market release product quality surveillance could be a phase of its own. In such phase the manufacturing yield of the product could be further increased and the cost could be further decreased.

III. OUTLOOK FOR THE MEDICAL DEVICE INDUSTRY

In the next decade, medical technology innovations will fundamentally transform the health care landscape, providing new solutions to address chronic diseases and revolutionize the way treatments are administered.

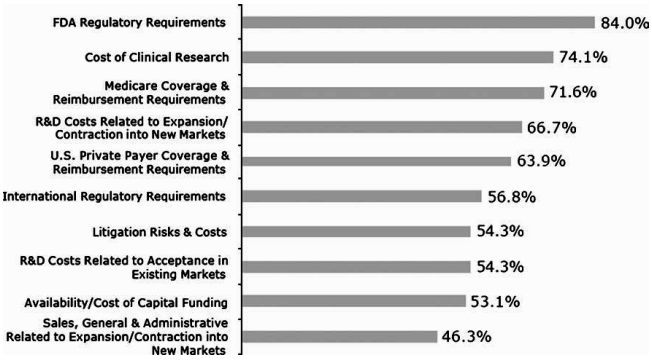

Fig. 3. Top ten factors that in 2003 affected companies' ability to develop new medical technologies over previous five years.

Figure 3 ranks the main factors that rein the industry's ability to bring new devices to market [4]. Given the long time required to obtain a FDA approval and the effort and resources that go into it, regulatory concerns top the list for 84% of the surveyed companies. Similarly, it does not come as much of a surprise that the cost, the time and the resources required to run a clinical trial represent the second highest concern for 74.1% of the surveyed firms.

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