Successful Medical Device Development: Critical Factors

Developing a new medical device is an exciting and demanding process. You have come up with an idea, may have made a prototype, filed your patent and are ready to undergo full development. Did you know that in the United States there are over 75 original PMA applications and 250 510(k) submissions per month to the FDA? The FDA currently has over 550 PMA devices under review. You have a lot of competition!

The rules covering medical devices development are not only issued by the FDA and other regulatory agencies but also by professional organizations such as the International Organization for Standardization (ISO), American Society for Testing and Materials International (ASTM), and Institute of Electrical and Electronics Engineer (IEEE). They all have their own standards which are necessary to abide by in order to obtain approval and remain competitive. However, these standards do require an excellent knowledge base to ensure proper implementation.

Few companies are in a position to manage the entire process strategically and tactically without external help and guidance. Product development from targeted market profile to post-marketing safety surveillance requires effective cross-functional teams and multiple hand-offs to support product transfer toward a successful commercial implementation. Furthermore, even if a product has received FDA market approval, company revenues are still not guaranteed and further upstream marketing and vigilance is necessary post-market approval. Commercialization of a medical product from its inception to an approved product in the hands of physicians is a true journey for the inventors and the company. This journey does not have to occur alone!

Very few companies can maintain the entire knowledgebase and infrastructure for a full developmental and approval process in today’s economy. A common business model is to get initial input on regulatory, developmental/testing and marketing strategies and then outsource tactics and operations. The usual issue with this model is a disjointed implementation of a product development strategy. Often the Medical Device companies
have consultants and service providers that are not networked, do not function as a team, and as a result, are not familiar with the full developmental program for the product.

We have formed **Reliance Medical Consortium**, an *alliance of companies*, to provide integrated, complementary, and critical services and consultation to the medical device community. Our consortium helps companies get through the multitude of business issues by relying on our recommended members for continuity. Reliance Medical Consortium is flexible and companies always have the choice to implement other consultants within the team as needed or forego services from some of our team members. Each member of the Reliance Medical Consortium has expertise and experience in strategies and tactics for optimal device development. Through our relationships, members of the consortium can provide optimal guidance and references for additional steps in the development pathway. Most importantly, the consortium members are industry experts who have had the experience on getting products approved and will work together to optimize interfaces and provide a smooth plan for clients. Such a strategic partnership will allow Medical Device companies to have a key source of contact for a variety of service providers, from concept to commercialization of a medical device.

The development pathway includes concept development, product target profile, product differentiation, and design recommendations for manufacturability and marketability. This information is used to support subsequent decisions on regulatory pathways, manufacturing, quality, and risk evaluations. Key success factors may include engineering evaluations, animal and human factor testing, and clinical trials programs as necessary. It is critical that each part of your development program mesh firmly with the other components, leading to a comprehensive 510(k), IDE or PMA submission to the FDA.

The following sections are examples of some of the critical activities to consider during successful development of *de novo* or substantially improved Class II and III medical devices that may need full development programs with the FDA.
1. **MARKET DATA:**

In any development plan, critical data is needed to support sound decision making. **Data Decision Group, Inc.** provides market sizing quantitative/qualitative technology assessments and evaluation of new technologies and opportunities, and assesses prospective acquisitions. For instance, one rapidly growing medical device segment is cardiovascular, and the following section provides an example summary of the data that would support a business or development plan:

**Key Finding:**

The Global Cardiovascular (CV) Device Market is one of the largest segments in medical devices and is projected to reach $54.3B by 2015 (Table 1)\(^1\).

**Why this is important:**

All Medical Device companies benefit from development in the CV space because an increase in CV procedures drives the use of a wide range of medical products. In addition, a segment of these patients may improve enough to have other procedures, such as knee repairs, etc. However, there are risks associated with many of the products that are developing “blockbusters” in the CV device segment\(^2\). For example, according to the Wall Street journal, in the left ventricular assist device (LVAD) space, there may be adoption risk due to the early stage of product evolution. This is because patient candidates for an LVAD are usually quite sick. When physicians consider patient eligibility for an LVAD, they must also consider the invasiveness of the procedure.

Among the usual suspects for the increase in LVAD are an increasing prevalence of cardiovascular diseases, an aging population, and the introduction of innovative products. Two new drivers are the increasing prevalence of co-morbidities like diabetes and obesity, and emerging markets outside of the US.

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\(^1\) Global Cardiovascular Devices Pipeline Landscape: Analysis of Key Upcoming Products and Technologies, Global Data, 2010

\(^2\) Investor Downside Risks for Cardiovascular Devices a Topic in WSJ Transcript Medical Devices Report, April 28, 2009
Top Trends in CV:

- MRI Compatible Cardiac Rhythm Management
- Minimally Invasive Technology to drive valve replacement in high risk patients
- Bioabsorbable stents
- New coating technologies to reduce stenosis
- Bio-engineered stents to quickly heal sclerotic tissue
- New improved diagnostic tools & technologies, e.g. Intravascular Ultrasound System (IVUS)

Table 1: CV Devices, Global Revenues, (000)$

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<tbody>
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<td>CRM</td>
<td>$14,003</td>
<td>$14,852</td>
<td>$15,776</td>
<td>$16,818</td>
<td>$17,460</td>
<td>$18,664</td>
<td>$20,024</td>
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<td>IC Devices</td>
<td>$10,777</td>
<td>$11,354</td>
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<td>$12,802</td>
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<td>PV Devices</td>
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<td>EP Devices</td>
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<td>Heart Valves</td>
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<td>$1,270</td>
<td>$1,332</td>
<td>$1,402</td>
<td>$1,472</td>
<td>$1,561</td>
<td>$1,662</td>
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<td>Cardiac Assist</td>
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<td>$1,134</td>
<td>$1,223</td>
<td>$1,329</td>
<td>$1,451</td>
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<td>$2,326</td>
<td>$2,452</td>
<td>$2,595</td>
<td>$2,750</td>
<td>$2,935</td>
<td>$3,145</td>
<td>$3,335</td>
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<td>CV Monitor./ DX Devices</td>
<td>$727</td>
<td>$764</td>
<td>$806</td>
<td>$853</td>
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<td>All CV Devices</td>
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<td>$47,770</td>
<td>$51,388</td>
<td>$54,743</td>
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CV Growth is Global; High Growth Expected in Asia

There is high opportunity projected for the Asia Pacific (AP) Drug Eluting Stent (DES) market. While the Japanese market remains the largest in AP, China is the second-largest

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3 Global Cardiovascular Devices Pipeline Landscape: Analysis of Key Upcoming Products and Technologies, Global Data, 2010
market, and its size is expected to exceed the Japanese market, with expected growth of almost 15% through 2014. Although Asian markets have lower per capita healthcare expenditures than the US and EU, they are expected to be the future growth markets of the health services industry⁵.

For example, the approval of new DES in China is generating a high level of marketing activity at interventional cardiology, device and drug manufacturing companies. The opportunity for DES revenue in China is significant, driven by:

- Increasing prevalence of coronary artery disease in the country
- Growing rates of co-morbidities such as diabetes and obesity
- A growing elderly population
- Trend towards unhealthy lifestyles (poor dietary habits, smoking)
- Dramatic growth of the middle class in urban areas
- A substantial increasing number of Chinese are now expected to be able to afford costly, non-reimbursed medical procedures

The worldwide recession has caused many Medical Device companies to pull back to more conservative strategies. However, real growth opportunities exist for those

⁵ Business Insights, March, 2009
companies willing to invest in future growth, and non-traditional strategies. As you can see, this detailed information along with a competitive analysis can provide any program the materials to evaluate potential market success.

2. MANUFACTURING

Another critical decision in the development of new products is one that concerns the aspects of manufacturing and quality management. The company, Bavaria Medizin Technologie, GmbH (BMT) is a leader in original equipment manufacture (OEM) and Contract Product Development. As a key consideration for any aspect of design and scale-up process of medical devices, three critical factors would impact the amount of time to get a product to the point of commercial launch.

A) Level of staff expertise
B) Use of technology
C) Product manufacturability

Staff expertise is a primary factor in driving project timelines. Experienced staff can manage a project well (i.e. generate value while reducing costs), by applying its expertise, and leveraging its professional network to find solutions to problems. Most medical device manufacturers are not vertically integrated; so not all expertise is in-house. Knowing whom to tap (and how much) is important in reducing timelines.

Class II and Class III devices often require the integration of multiple technologies. Project management skills become very important in keeping the project aligned with its targeted objectives and costs. Concentrated focus is required intermittently, and good project management skills help manage these variations in resource demand. For instance, when setting up for manufacturing (e.g. design transfer, process validation, etc.) a significant amount of testing is required at the beginning to understand product robustness, but once in production the demand on resources is reduced. An experienced staff manages this process efficiently using the right labor, processes and equipment.

Poor budgeting hampers progress in controlling manufacturing quality or driving continuous improvement. In situations like this, engineers will “band-aid” problems rather than fixing them, and quality suffers. Manufacturing of Class II and Class III devices is CAPEX (Capital Expenditures) intensive, and maintaining the project timeline
is sensitive to the manufacturing spending decisions. Because of all the technologies that are integrated in the development of medical devices, there is a need for “the right tool to do the right job”. For instance, a simple manufacturing of balloon-catheter as stent delivery system would require an estimated $1.5MM to $3MM in CAPEX per production line for low volume (excluding custom designs and manufacturing overhead). Company management needs to be ready to spend money at the appropriate time in acquiring equipment (new or used), designing fixtures, and developing processes. Using corporate budgeting tools, manufacturing spending should be well analyzed with proper allocation for capital expenditure.

Product manufacturability is another key factor. The initial ASP during first product commercialization is usually the highest price attainable; but over time, price pressure and competitive forces will drive it down. To maintain gross profit margin, COGS (Cost of Goods Sold) should follow a similar downward trend to compensate for revenue loss. A well-designed product incorporates a predictable and planned reduction in COGS over the product life cycle. Using design for manufacturability guidelines, a significant reduction in COGS could occur throughout the product’s manufacturing life. Product re-design while in manufacturing is expensive (due to increased costs for testing for design verification and validation), not to mention R&D resources that have to be allocated to unexpected changes rather than new product development.

These factors impact gross profit margin. Despite a stellar manufacturing facility, if a product is too complex to build or poorly designed, value is not created.

3. ENGINEERING TESTING

The engineering and design of any medical device is dependent on proper engineering testing with multiple feedback loops into the design and manufacturing stage. According to its clients, Orthokinetic Technologies (OKT) and OrthoKinetic Testing Technologies LLC (OKT²) are the finest “full-service” medical device testing enterprises in the world. For any medical device company, services that provide the guidance and pre-IDE strategies for assessing the safety and effectiveness of novel medical device technologies to perform medical devices testing is critical. Such testing is required to meet strict regulatory and quality standards in bringing the device from the
design/prototype phase through the FDA approval phase. OKT\textsuperscript{2} is a primary provider to Medical Device companies from the design stage through development, testing, and FDA submission for high quality medical device testing and innovative technology development. OKT and OKT\textsuperscript{2} are a full service medical device testing facility capable of handling all feasibility and regulatory testing in accordance with ISO and ASTM standards.

Before initiating a project, it is important to discuss the testing and FDA strategies to evaluate, justify and validate all of the testing needed on a medical device to determine if it is safe and effective. During engineering and manufacturing stages of development, the risks must be evaluated and verified using tools like risk maps and formal failure analyses that will be included in the regulatory submission. Included in the risk mitigation processes to evaluate novel technologies may be strategies for evaluations of wear particulate measurements, \textit{in-vivo} animal or cadaveric studies for testing functionality, tissue responses, and surgical logistics. For this aspect of the project, medical device manufacturers require a partner with experience and knowledge to manage overall testing strategies.

Important considerations for the development of any Type II or III medical device, services that can be provided by OKT or OKT\textsuperscript{2}, are:

- FDA regulated testing to evaluate the mechanical performance of orthopedic implants including testing of ASTM and ISO standards
- Computer aided design (e.g., drafting, solid works and finite element modeling—simulation in-situ spine models)
- Finite element analysis (FEA) for pre and post implant verification and validation stages, proven in the development of products for the musculoskeletal system
- Feasibility testing through early bench top design tests
- Biomechanical evaluations of performance in the musculoskeletal system
- Wear testing with state of the art six-degree of freedom wear-testing
- Full material and particulate characterization capabilities
- Collaborative partnership with local vivarium and world renowned veterinarian
• Smart sensor development, testing, and validation for smart devices, programmable pumps and devices, and systems.

4. ANIMAL TESTING

Performance data are often needed to help demonstrate that the proposed device is safe and effective. These data may include results from engineering, bench, design verification, human factors, animal, or clinical studies. The regulations and risk management standards recommend that the safety and efficacy studies should be conducted in a manner as similar as possible to how the device will be used during routine application. The necessities of different tests are based on risk analysis. This means that Medical Device companies need to understand the implications and potential critical success factors for conducting the appropriate animal and human surgical research, procedure development, and even training of surgical services. Each of these are critical success factors during development that can enhance the approval process and marketability for your device. The FDA has made it clear that the animal studies utilized for the assessment of medical devices typically have to be conducted under GLP and quality management systems, and provide initial evidence of device safety, potential performance parameters when used in a living system, and the biologic response that a living system may mount towards the device. The FDA has just issued a new guidance document for considerations of animal studies for cardiovascular devices. The FDA guidances and regulations dictate that companies provide rationale for the selection of particular animal models for each animal study with a clear decision analysis flowchart for this determination. The protocol needs to take into consideration the type of animal most relevant to the disease conditions and the animal and its related physiologic attributes which would provide a test system that offers a best opportunity at simulating the clinical setting. The rationale should clearly state the elements of your risk analysis that will be addressed by the model and why the particular animal model was selected. If there are limitations to the animal model such that the risks of the device are best addressed by bench or cadaver testing, these relationships should be described. The
Reliance Medical Consortium can provide Medical Device companies solutions to satisfy these requirements in line with the other conditions and testing.

5. CLINICAL TESTING

The FDA has strongly indicated in the 510(k) Working Group Preliminary Report and Recommendations (August 2010) that more medical devices will need clinical and quality evaluations. In addition, the recommendations include improving overall safety by requiring companies to provide reviewers with any scientific information known regarding the safety and effectiveness of the device at the beginning of the submission process. Clinical trials for medical devices have unique challenges that differ from pharmaceutical clinical programs. The ISO 14155 standard, "Clinical Investigations of Medical Devices in Human Subjects: Good Clinical Practices", differs from the ICH E6 and FDA 21 CFR Part 812 (Investigational Device Exemptions) and Part 312. The company needs to understand the implications of these different rules and regulations.

For some 510(k) submissions and most PMA applications, clinical performance data is required to obtain clearance to market. In these cases, conduct of the trial must be done in accordance with FDA's IDE regulation. The IDE (Investigational Device Exemption) regulations on clinical trials currently require justification of the investigations as well as a complete protocol, monitoring plans and informed consent sections. The protocol needs the following methodology sections:

- Objectives, hypothesis to be tested, or question to be answered
- Description of the type of trial (i.e., controlled/open, double-blind/single-blind, etc.)
- Detailed description of the conduct of the trial
- Description of statistical methods
- Case report forms
- An analysis of the protocol demonstrating its scientific soundness
- Description and analysis of all increased risks to the research subjects
- Manner in which risks will be minimized
- Justification for the investigation
- Description of patient population, including number, age, sex and condition
The clinical evaluations for medical devices thus require a thorough knowledge of the strategy and operational aspects that are unique to conducting clinical trials specifically for medical devices. In some cases, the Medical Device company may choose to abide by both the IDE and the ISO 14155 standards to comply with some European Community (EC) requirements in addition to the FDA requirements. Clinquest, Inc. has extensive experience in this area and will be able to provide the protocol strategy and design, project management, medical and clinical monitoring, Data Safety Monitoring Boards, medical writing, statistics and data management, and safety event reporting.

6. REGULATORY FILINGS

When working with regulatory boards like the FDA, you need someone that has had extensive interaction with the FDA and understands the current regulations. However, every regulatory application and meeting is a team effort and Clinquest, Inc. has the experience to work within the consortium for regulatory filings, talk with the FDA, prepare teams for meetings (such as the pre-IDE meeting), and work with the client and the client’s contractors to strategize on the submissions. They can then assemble and manage the application team from the various providers such as those described previously. The regulatory applications for a Class II device can be submitted either as a 510(k) or as an IDE prior to a PMA submission. The IDE, 510(K), and PMA applications have extensive required sections that are typically written by the development teams; and these teams need to have excellent communications and project management. This is a key consideration for the Reliance Medical Consortium when working together.

Even as a product is approved, there are key postmarketing surveillance requirements that need to be fulfilled. The 21 CFR Part 822 and ISO 14971 defines that a company needs to have a Postmarketing Surveillance Plan, which includes a component of having a method of collecting complaints, inquiries and safety events and a clearly defined method to track these records and the ability to act on this information. Clinquest, Inc. has a full medical information call center available to work with quality control departments to manage medical device complaints, inquiries, and medical device safety reports (MDR)
and help companies nearing approval or even submitting type II or III products for 510(k) or PMA.

7. CONCLUSION
When considering clinical and regulatory programs, you need a team that has an understanding of the key success factors that have implications during the design and development stages that will affect the efficacy, safety and risk, and consequentially the approval and marketability of your product. By having an association of service providers from the Reliance Medical Consortium that are cooperatively working with the client, the communications are clearer and the transition from one consultant or contractor to another is reduced. Each of the service providers in the Reliance Medical Consortium has in-depth experience in the various aspects of development and all have the experience to contribute and organize successful development plans and strategies.

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