US Medical Device Innovation: Moving from the Bench to Market

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***Abstract*— Many good ideas never make it to market. That is particularly true in the medical device sector. Commercializing products in a highly regulated market offers reduced competition, but increased burdens translating inventions into innovations. One important, often misunderstood, requirement is the regulated product engineering development process. Ignoring or misunderstanding this process increases economic, technical and operational risks, undermining valuation and return on investment capital. Alternatively, proper implementation yields higher quality, shorter time-to-market, lower total costs, and greater value.**

I. INTRODUCTION

THERE are tremendous clinical opportunities that need better solutions, especially given the aging United States (US) population, changing US healthcare economics, and transition to electronic-based processes. But the path from the bench to the market is fraught with pitfalls. From a medical device entrepreneur's perspective, access to capital, engineering talent, and pay-for-performance reimbursement are critical concerns. From an investor's perspective, risk predictability (time-to-market, capital turnover, and valuation) is a crucial criterion.

One approach is to take the invention to an established Food & Drug Administration (FDA) regulated company; the returns are better than failure, but not nearly as good as success. Another approach is to create a start-up to commercialize the invention. How you approach the risk/reward calculation for these and various intermediate commercialization alternatives depends on your personal ethos, as well as your technical and business background. What does not depend upon these is that medical device innovation is highly regulated in the US. This is the cost side of the benefit of significantly reduced competition in the enormous US medical device market (> 10^{11} US$) [1].

Inadequate understanding of US federal regulatory requirements imposed on the medical device engineering *development* process (not the submission process) is a major impediment to innovation and a primary risk factor highly correlated with innovation failure. Valuation (from both the entrepreneur's and investor's perspective) needs to include not only past accomplishments and the present opportunity, but also the relative risk of correct or incorrect regulated product development. Properly implemented, correct engineering development is more rapid, less costly, and offers a higher degree of successful innovation, making the opportunity a more attractive investment choice.

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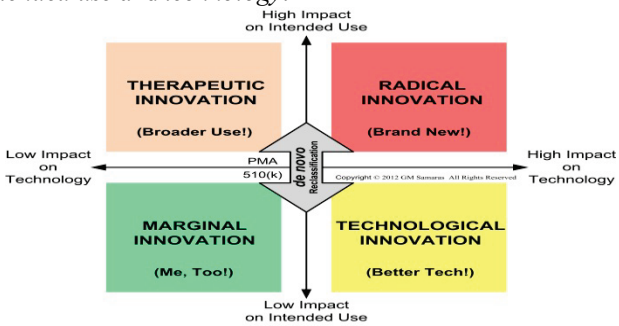
II. MEDICAL DEVICE INNOVATION & US REGULATION

Innovation is not synonymous with invention. Innovation presupposes invention but requires development transformation to a product, process or service, and then dissemination (usually by commercialization) [2]. There are different types of innovation (technical, market, and administrative); here, we focus on technical innovation.

Medical device marketing in the US is primarily regulated by one of two means: premarket notification (known as the 510(k) program) for Class 2 devices and premarket approval (PMA) for Class 3 devices. Figure 1 shows a modification of the Henderson & Clark [3] model of product innovation in the context of US medical device regulation (it excludes the lowest risk Class 1 devices). US medical device regulation is risk-based and strongly depends upon two product attributes: *intended use* and *technology*.



LEVEL OF INNOVATION	REGULATORY APPROACH	UNCERTAINTY ABOUT SAFETY & EFFECTIVENESS	TESTING REQUIREMENTS
MARGINAL MINOR	Administrative Clearance (510k)	VERY LOW LOW	Consensus Standards & Special Controls
MODERATE MAJOR	PreMarket Approval (PMA)	HIGH VERY HIGH	PLUS Supervised Clinical Trials & Special Audits

Fig. 1. Medical Device Innovation & US Regulation

- Medical devices that are clones of existing, legally marketed medical devices are marginal innovations (e.g., one more transcutaneous electrical nerve stimulator or one more noninvasive blood pressure monitor); they are "me, too" devices offering little that is new. If they have essentially the same technological characteristics as their claimed predicate [4], they have a very low level of uncertainty regarding how to establish reasonable safety and effectiveness. They are regulated by the 510(k) program.
- Medical devices that use new technology (e.g., change in materials, energy source, hardware, software, and/or human factors design [4]) to accomplish the same intended use of existing, legally marketed medical devices are technological innovations. When they have low uncertainty regarding establishing reasonable safety and effectiveness, they also are regulated by the 510(k) program. If not, they

are reclassified and regulated by the PMA program.

• Medical devices that use essentially existing medical technology for a new intended use (e.g., ophthalmic surgical lasers) are therapeutic innovations. They have a high level of uncertainty regarding establishing reasonable safety and effectiveness for the new intended use. They are regulated by the PMA program.

• Medical devices that use new technology for a new intended use (e.g., implanted pacemakers, HIV test kits) are radical innovations. They have a very high level of uncertainty regarding establishing reasonable safety and effectiveness and are regulated by the PMA program.

Typically, although not always, the disruptive new product ideas show up in the therapeutic or radical innovation categories, both of which are regulated by the PMA program. The PMA program (please refer to Figure 1) differs from the 510k program in a two important attributes. The 510(k) is an administrative clearance for marketing, whereas the PMA is federal scientific and medical approval of a product. The 510(k) requires establishing reasonable safety and effectiveness using testing specified in consensus standards and certain FDA special controls; the PMA requires FDA-supervised clinical trials plus special premarket audits of product development, product manufacturing, and other company practices & procedures.

Regardless of whether your medical device is a marginal or radical innovation, there are two important engineering considerations when developing your product. There is a specific, non-discretionary, engineering development paradigm applicable to medical devices and that development process must implement Design Controls and Risk Management prior to the onset of product design.

III. Medical Device Development

The development of medical devices is not an arbitrary process, subject to personal discretion; it is specified in FDA's Quality System regulation (QSr) [5] and an international consensus standard (ISO 13485) [6] and is elaborated in various FDA guidance documents. Ignoring or misunderstanding this has historically resulted in innumerable, unnecessary difficulties often leading to delays or failure for medical device entrepreneurs. A recent FDA report indicates that for the period 2001-2009 even though medical device revenues only doubled, serious adverse events nearly quadrupled and (for 2003-2009) failures in product design caused nearly a third of product recalls [7].

A. Regulated Product Development

Figure 2 is a high-level view of the medical device commercial development process. This schema is a medical device innovation standard operating procedure from invention at the bench through product launch into the US market.

It begins with knowledge acquisition (basic and applied research) followed by development of an innovation strategy, as expressed in a business plan and a high-level project plan. It is at this point (Gate #1: Strategy Approval) that most funding decisions are made for commercial product development. Of particular concern going forward are (a) the correctly-timed initiation of Design Controls and Risk Management to comply with US Federal regulations and international standards and (b) the development of specific documents required for 510(k) or PMA submissions and subsequent FDA periodic inspections.

Design control and risk management activities must start before any commercial design begins. This way, no "legacy" design survives that was not subject to design control and risk management. This absolutely includes commercial feasibility and proofs of concept designs, whose uncontrolled designs too often are the basis for future liabilities in the commercial product. This is an especially acute problem in the case of mechatronic medical devices that rely on software for their sophisticated functionality.

Commercial development consists of three major phases: (a) Basic Design to determine commercial feasibility, (b) Prototype Building to determine product economic and technology requirements, and (c) Pilot Production to determine manufacturing, distribution, and servicing requirements. It is during this latter phase that final testing is completed and regulatory submissions are made. Once cleared or approved, commercialization begins (Gate #5: Launch Approval) and cash flow will reverse polarity.

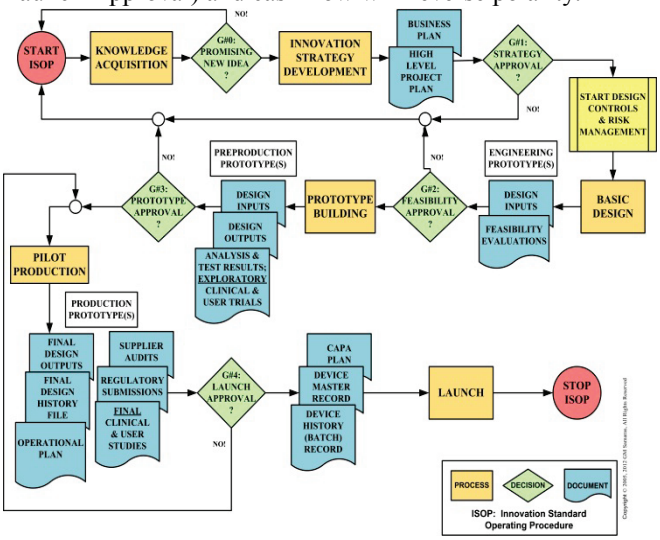


Fig. 2. Device Development Schema. Adapted from [8].

B. Design Controls

Figure 2 appears to depict the development process as linear, when it is actually highly iterative. The iterative nature may be more clearly seen in Figure 3 where the fundamental elements of Design Controls are identified. Development planning is omitted from Figure 3 for clarity, but is partially captured in Figure 2 (business plan and high level project plan).

Design Controls are nothing more than the fundamental elements of classical systems engineering [9]. This nearly century-old engineering paradigm has been repeatedly proven in a wide range of industrial sectors (e.g., aerospace,

defense, automotive) and provides the most economically and technically efficient and effective means of getting a product to market. Proper implementation offers an efficient means of developing safe and effective medical devices. Poor or incomplete implementation results in a development process with increased economic, technical, and operational risks, creates both premarket and postmarket regulatory difficulties and corporate liabilities, and stifles innovation and returns on investment capital.

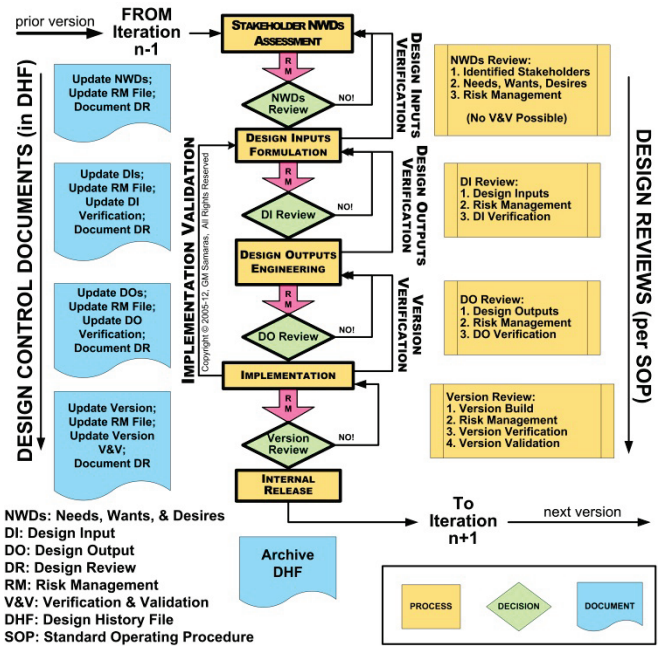


Fig. 3. Design Controls. Adapted from [8]

Figure 3 identifies both the process elements and the documentation requirements specified in the QSr and ISO 13485. In addition to the technical process elements (stakeholder assessments, design inputs or *requirements* formulation, design outputs or *specifications* engineering, and version building), the diagram also identifies the specifics of the design review process. Design reviews are one of four critical engineering process elements and are equal in importance with risk management, engineering verifications, and validation (addressed in following sections). These four are internal error-correcting mechanisms in the engineering development process that are central to the efficiency and effectiveness of the process. The formalized design review functions as a powerful means of ensuring adequate communication and coordination among developers, management, and other stakeholders. Defective design reviews are a primary cause of failures in risk assessment, verifications, and validation.

C. *Errors & Risk Management*

Errors, especially those leading to safety issues and reduced profitability, are the bane of our existence. Figure 4 separates human errors into two categories of particular interest for engineering development. It associates four types of human behavior (expected, unexpected, misguided, and malicious). The four types of Individual User errors are well-known: routine use, novel use, misuse, and abuse. Three of the four types of System Use errors (active, latent, and drift errors) are not so well-known outside of the human factors and ergonomics community. The first two (active and latent errors) were defined by Reason [10] and correspond loosely to "known bugs" and "unknown bugs", respectively. The third (drift errors) was defined by Dekker [11] and corresponds to an unintended transition of the system beyond its designed safety envelope (a drift towards failure).

	ERROR CATEGORY	
ERROR TYPE	**SYSTEM USE**	**INDIVIDUAL USER**
EXPECTED BEHAVIORS	ACTIVE (KNOWN BUGS)	ROUTINE USE
UNEXPECTED BEHAVIORS	LATENT (UNKNOWN BUGS)	NOVEL USE
MISGUIDED BEHAVIORS	DRIFT (BEYOND DESIGN ENVELOPE)	MISUSE
MALICIOUS BEHAVIORS	SABOTAGE	ABUSE
	LOCUS OF CONTROL: *DEVELOPMENT, DEPLOYMENT, & MAINTENANCE ORGANIZATIONS*	**LOCUS OF CONTROL:** *INDIVIDUAL HUMAN USER(S)*

Fig. 4. Use versus User Errors. Adapted from [12], [13].

How do you avoid system use errors and reduce the probability of end-user errors? Focus risk management on both internal operational risks as well as external end-user risks. Risk management is the second critical process element and is required by both the FDA's QSr and ISO 13485; it is depicted by the red arrows in Figure 3. ISO 13485 specifically cites ISO 14971 [14]; it is the risk management consensus standard for medical devices and a FDA-recognized standard. Risk management is a requirement of federal regulation and the international standard; it is also good business practice, whose purpose is to protect stakeholder value. Figure 5 shows the process is iterative, consisting of only three repeated activities: *identification*, *assessment*, & *mitigation* of risks. Improper application of risk management (e.g., only at the beginning or only at the end of development) negates its value as a mechanism for internal error correction. To be effective, it must be applied to hardware, software, human factors, and overall system design – of both the product and the process of developing the product. If the development team is not designing for manufacturability, if the software developers are not using modern software engineering principles and practices, and if there is not a focus on reliability, then you can be assured of future economic, technical, and operational risks.

Fig. 5. Risk Management

D. *Verifications & Validation*

Verifications and validation are the last two of the four critical process elements and often seem to pose conceptual difficulties for many medical device developers. In medical device design control, validation means that you developed the *right system* (the developers correctly solved the problem captured by the design input process); verification means that you developed the system the *right way* (the developers

did their job correctly at each step of development).

		Discriminating Verifications & Validation				
			Inspection	Analysis	Measurement	Demonstration
Design Verifications	Systems Engineering	Verification 1 (Requirements)	☑	☑		
		Verification 2 (Specifications)	☑	☑	☑	
		Verification 3 (Version)	☑		☑	
	Risk Mgmt.	Verification 4 (Application)	☑		☑	
		Verification 5 (Risk Reduction)		☑	☑	
Design Validation						☑
			Trace Checks, Design Reviews, Walkthroughs, & Formal Inspections	Formal or Mathematical Analyses & Simulations	White Box Testing In Laboratory Setting	Black Box Testing with Users in Use Environment

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Fig. 6. Verifications versus Validation

Verifications are internal error-correcting mechanisms in the engineering process that reduce the probability of translation errors during development. Figure 6 shows that, while there can only be one type of design validation, there are five (5) different types of design verifications. Three types of design verification are from systems engineering (requirements, specifications, and implementation [9], see also Figure 3). The other two types of design verification are from risk management [14]; verification that you properly applied your proposed mitigation and verification that your properly applied mitigation actually reduced the targeted risk. These risk management verifications are not explicit in Figure 3; they are buried in the red arrows and are documented as part of the risk management file.

Unlike design verifications, design validation ensures you developed what your stakeholders asked you to develop (documented in the design inputs) – did you develop the *right system*? Design validation can occur at the system level, subsystem level (e.g., software validation), or module level (e.g., validation of 3rd-party modules designed for interoperability). System validation is the medical device manufacturer's final defense against Type III errors: "correctly solving the wrong problem". Poorly designed or improperly executed "validation" studies negate its value and provide the manufacturer little or no benefit.

IV. Medical Device Mechatronics Maturity

Mechatronic medical devices are an important historical innovation in healthcare. These devices integrate sensor and effector mechanical & electrical hardware with information-driven software processes into a potentially synergistic whole, offering increasingly sophisticated functionality. They range the gamut from simple positioning systems to infusion pumps, robotic surgical devices, *in vitro* diagnostic device readers, and healthcare information technologies.

While the use of mechatronics offers enormous potential for increasingly sophisticated functionality, it also presents equally large *quality* problems with interdisciplinary development [7]. These are not merely technical issues (e.g., promoting integration of hardware and software development by automatically generating a new hardware abstraction layer with each new hardware revision), but also organizational issues (e.g., preventing development from occurring in independent silos [15]) and project management issues (e.g., emphasizing and prioritizing quality milestones over schedule and budget milestones [16]). How a medical device development organization deals with the hardware, software, and all-encompassing human factors issues may be viewed as a measure of their *mechatronics maturity*.

Mechatronics maturity is: *how good your development process is at avoiding or recovering from the creation or propagation of System Use errors* (please refer to Figure 4). Testing (verifications and validation) is an outcomes approach to quality; it is necessary, but it is never sufficient. Quality engineers understand this well. Inspection alone historically has proven inadequate and, in the 20th century, quality management moved successively through statistical quality control, quality assurance, and strategic quality management [17]. This is the process approach to quality practices; it is an engineering management strategy that recognizes outputs are inextricably linked to inputs and transformations. The specific processes used by medical device development organizations help us estimate their mechatronics maturity ... and that is a predictor of new product development (NPD) quality and one reason why the FDA believes that quality system management audits have value.

			Mechatronics Maturity		
Stage	Goal	Behavior	Hardware (HW)	Software (SW)	Human Factors (HF)
5	Strategic	Continuous Improvement	Human-Centered Systems Engineering		
4	↑	Quantitative Management	Integrated HW-SW Systems Engineering		Stakeholder Dissonance Management
3	Tactical	Defined & Proactive	HW Systems Engineering	SW Systems Engineering	System Usability Engineering
2	↑	Qualitative Management	HW Engineering	Computer Science	Developer-centered Usability
1	Uncertain	Ad Hoc & Chaotic	Trial & Error	Computer Programming	Huh?

Fig. 7. Medical Device Mechatronics Maturity Model

Figure 7 shows one means of assessing an organization's mechatronics maturity [18]. As with other estimates of organizational maturity [19], it can be envisioned in five discrete stages. From a goal-directed perspective, they range from uncertain (no clear goal) through tactical to strategic orientations. Organizational behavior ranges from *ad hoc* and chaotic all the way to a quantitatively-managed organization focused on continuous improvement.

Why should mechatronics maturity be of concern to the medical device entrepreneur and investor? It directly impacts economic, technical, and operational risk. NPD presents a set of engineering management tradeoffs among the four basic NPD attributes: *budget, schedule, scope,* and *quality*. A low maturity NPD process is more costly and less time efficient; trading off scope and quality against budget and schedule will reduce market share and increases future liability. A high maturity NPD process is quite cost and time efficient, permitting the developing organization to focus on maximizing scope and quality … and market share.

V. Discussion

An understanding of regulated product engineering development as expressed in the business plan, project plan and staffing should be an important determinant of valuation. An incorrect or inadequate engineering process invariably will result in regulatory and other difficulties due to a lack of required development artifacts and requisite testing necessary for demonstrating reasonable safety and effectiveness. Even in those cases where a device has "slipped" through the 510(k) clearance process, there are still adverse sequelae. Consider the following two examples – one regarding the occurrence of adverse events and the second regarding expanding the indication for use (and the market potential) for a cleared medical device.

In the last decade, there has been significant publicity regarding medical devices (e.g., general hospital, gynecologic, orthopedic, etc.) that have been cleared through the 510(k) program and subsequently associated with significant serious adverse events. Unlike Class 3 devices, Class 2 devices do not benefit from express federal preemption. A simple means of supporting negligence, possession of unsafe features, or lack of necessary features for safe intended use is absence of, or significant flaws in, requisite engineering development artifacts (e.g., design reviews, risk analyses, verifications, and validation).

As clinical knowledge increases, opportunities arise for expanded intended use of existing medical devices. Medical devices differ from drugs and biologics, in that safety testing for the latter is always systemic (administering a drug or biologic typically subjects the whole body to its actions). In the case of medical devices that have been cleared through the 510(k) program, there typically has been little or no *in vivo* human safety testing prior to clearance. Consider the example of a transcutaneous electrical nerve stimulator (TENS). There are about 150 manufacturers world-wide; those marketed in the US have been administratively-cleared over the years through the 510(k) program. There are published clinical indications that TENS has value in wound healing, a market significantly more lucrative than for temporary symptomatic pain relief. At present, Medicare & Medicaid will not reimburse TENS treatments for wound-healing, because TENS has not been approved by the FDA for that intended use. What is preventing manufacturers from pursuing this new intended use? It cannot be the cost of going through a PMA (including the requisite clinical trials); a quick economic analysis demonstrates that the potential benefit far outweighs the cost.

In all likelihood, what is preventing this therapeutic innovation is the absence of evidence that the existing medical device hardware, software, and human factors engineering were conducted compliant with the current regulated product engineering development paradigm. The artifacts to support the reasonable safety and effectiveness acceptance criteria for the approval of the new intended use by a PMA do not exist. Failure to meet these requirements then has adverse ramifications for the continued sale of the already 510(k)-cleared device. And this is merely one instance of many possible expansions of device intended use.

VI. Conclusion

Many good ideas don't survive the journey from the bench to market. This is especially true in a highly regulated marketplace. There are many factors that are beyond the control of the entrepreneur and the investor. One critical factor that is within both the entrepreneur's and the investor's control is whether or not the correct regulated product engineering development process will be followed. How well or poorly this is planned, executed, and documented is a strong predictor of successful medical device innovation.

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