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THE ITERATIVE NATURE OF MEDICAL DEVICE DESIGN

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ABSTRACT
A one-year study, sponsored by The Institute for Health Technology Studies, was conducted by a team of Stanford University researchers to develop a linear model of the medical device development process, from concept to commercialization. The empirical field study involved interviewing and surveying individuals who had been involved with various stages of the development process, ranging from concept definition to post-market surveillance. Six medical device case studies were conducted to exemplify the device development process and its variations for different types of technologies. The focus of this paper is to examine variations to the linear device development model, specifically iterations that occur across development phases. Development variations for drug/device combination medical products and variations influenced by financial constraints are likewise explored. The data presented in this paper is intended to provide a foundation for creating new development models and guidelines which reflect the highly complex and iterative nature of medical device design.

Keywords: medical device development process, medical device design, iterative design

1 INTRODUCTION
The Institute for Health Technology Studies (InHealth) funded a one-year research study at Stanford University (from October 2006 to October 2007) to develop a model of the medical device development process, from concept to commercialization [1]. The study was motivated by the notion that a detailed understanding of the medical device innovation process could help inform future policy makers, and potentially help to streamline and accelerate the approval process for complex medical devices. In order to construct a general model of the medical device development process, a literature review and extensive field study was conducted. Six in-depth case studies covering a diverse range of medical technologies were also conducted, in order to further explore and exemplify the device development process.
Although the research revealed that an ideal linear device model is followed across multiple innovation settings, it became clear that, in practice, medical device development is often a highly iterative and non-linear process. The linear model is determined, in large part, by the FDA's Quality System Regulation (QSR), which provides a framework that device manufacturers must use when developing and implementing design controls. Yet, the exact practices used by device manufactures to implement design controls may vary by device type and other factors.
Therefore, the focus of this paper is to explore variations to the linear device development model, first in terms of iterations that may occur across development phases. Across-phase iterations of particular interest include the following: user feedback loops, pre-validation testing loops, verification & validation test iterations, intellectual property iterations, process validation and manufacturing iterations, regulatory and clinical trial loops, and limited market release iterations. The paper also explores device development variations for drug/device combination medical products, as well as development variations that are influenced by financial constraints. It is intended that the process variations explored in this paper should be regarded as an extension to the linear device development model, to be used by both device developers and future policy makers. The data presented provides a

foundation for creating new models and guidelines that are aimed to reflect the highly complex and iterative nature of the medical device development process.

2 METHOD

A literature review and empirical field study was conducted in order to construct a general model of the medical device development process, and to explore variations to the linear model. The research approach involved 'grounded theory' building to generate theory from the grounded experiences of study participants, rather than test pre-conceived beliefs and theories [2]. A detailed description of the process used to construct the linear medical device development model (MDDM) has been previously reported [3]. The methods used to explore variations to the general model will be described in this paper.

2.1 Literature Review

An in-depth review of the engineering, management, and medical literature, and an extensive literature search of appropriate databases (MedLine, GoogleScholar, FDA's website, and others) were used to identify and describe existing models for medical device and drug development [1,3]. Specific information concerning the different regulatory pathways for medical devices, and relevant aspects of FDA's Quality Systems Regulation (QSR) was collected and summarized from the literature and from publications and guidance documents published by the FDA's Center for Devices and Radiological Health [1]. A review of Standard Operating Procedures (SOPs) from four medical device companies (large, mid-size, and start-up) was also performed [3].

2.2 Empirical Field Study

The first part of the field study focused on the construction of a linear device development model and the exploration of variations to the general model. In the second part of the empirical study, six case studies were conducted to exemplify the medical device development process and its variations for different technology types.

Over 85 interviews were conducted in total over the course of this study, from November 2006 to September 2007. Interviewees from both parts of the field study consisted of individuals who had been involved with various stages of the development process, ranging from research and invention to early-concept definition, device development, regulatory approval and post-market feedback. Table 1 below shows the breakdown of interviewees by entity. About 30% of interviewees came from large medical device companies, and about 20% each from mid-scale and start-up companies, respectively. Figure 1 shows a breakdown of interviewees by geographic location and by functional area.

Table 1. Interviewee Breakdown by Entity

Interview Type		Number of Interviewees
Medical Device Companies	Start-up (Less than 5 yrs, 100 employees)	16
	Mid-scale company (700 - 6000 employees)	15
	Large-scale company (25,000+ employees)	27
Regulators	Food and Drug Administration (FDA)	13
	Centers for Medicare & Medicaid Services	1
Academic & Clinical Research	Physician Inventor	8
Financiers, Development & Consulting Firms	Incubator	4
	Venture Capitalist	1
	Angel Investor	3
	Consultant	2
Legal	IP Attorney	1

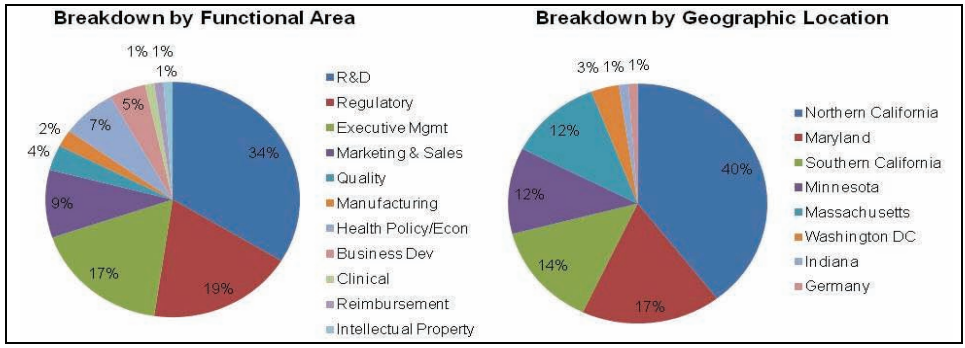

Figure 1. Interviewee Breakdown by Functional Area and Geographic Location

Variations to the Linear Model - Initial Interviews & Surveys

Variations to the linear device development model were determined through interview feedback and surveyed responses. Interviewees were first asked to review the linear device development model (shown in Figure 2) and to describe obstacles they may have encountered during the development process, both on a broad development level and specifically pertaining to their area of expertise. The goal was to understand and delineate typical iterative loops within the medical device development process. To support interview findings regarding model variations, an electronic survey was subsequently distributed to interviewees. In the survey, respondents were shown two examples of model variations (i.e. iterative development loops) and asked to describe variations they had experienced. Interviewees were also asked to define the development phases during which these variations occurred, and what functional areas were involved in the associated development activities.

Case Studies

Six case studies were conducted to illustrate the medical device development process and its variations for different types of technologies[1]. The goal in choosing the six technologies was to create a wide variety of technologies, covering various medical fields, different innovation settings, and different regulatory paths. Particular attention was spent on identifying patterns that illustrate various aspects of the development model, including variations to the linear model and iterative loops during development. Case studies were developed for the following technologies:

- FloTrac Sensor (Edwards Lifesciences): Large-company setting; diagnostic device; cardiovascular; Class II – 510(k); non-implant.
- Activa® Therapy (Medtronic, Inc.): Large-company setting; therapeutic device; neurological; Class III - PMA; implant.
- Oncotype DX Breast Cancer Assay (Genomic Health, Inc.): Start-up setting; in-vitro diagnostic; OB/GYN; lab-based and currently not (yet) regulated by FDA's Office of In-vitro diagnostics.
- Contak CRT-D cardiac resynchronization therapy (Boston Scientific, formerly Guidant): Large-company setting; therapeutic device; cardiovascular; Class III – PMA; implant.
- GuardWire® Temporary Occlusion and Aspiration System (Medtronic, formerly PercuSurge Inc.): Start-up setting; therapeutic (procedure-related); cardiovascular; Class II – 510(k); non-implant.
- Z.one Ultrasound Imaging System (ZONARE Medical Systems): Start-up setting; diagnostic imaging device; radiology; Class II – 510(k); non-implant.

[1] The case study method is especially appropriate for research in new topic areas and can contribute critical insights as well as identify important factors. See for example: Montoya-Weiss, Mitzi M., and Cantalone R. "Determinants of new product performance: A review and meta-analysis. Journal of Product Innovation Management 11:397-417, 1994.

In developing the case studies, interviewees from each company were asked to discuss the following topics: company background; technology background; sources and settings of innovation; type of innovation; key activities and decisions in the development process; regulation; reimbursement; current status of technology; and key insights.

3 RESULTS

3.1 Overview of Linear Device Development Model

The previously described linear device development model [1,3] is shown in Figure 2. This model identifies five major phases, separated by four decision gates. Pre-development activities occur prior to Gate I, development activities occur between Gates I and III, and product launch and post-market assessment occur in the phase following Gate IV. In the model, the major functional groups are identified in boxes on the left side of the chart. Major decisions are shown (in parallelograms) at the bottom of each phase. Upper level activities for each functional area are highlighted in boxes within each phase. The horizontal progression represents a generalized time-line. The major milestones/ gates can occur at different times in the development process depending on the type of device. The model describes a process that is most applicable to PMA and 510(k) devices that require some form of clinical data, but can also be simplified for 510(k) devices that do not require any clinical data for regulatory clearance.

The activities defined in the linear device development model are largely dictated by the FDA's Quality System Regulation (QSR), which is contained in Code of Federal Regulations, Title 21 Part 820 [4]. The QSR prescribes the elements of the design process, including definition of design input, design output, development, testing, risk analysis, and process qualification. Since the FDA recognizes that design controls must apply to a wide variety of devices, QSR does not prescribe the exact practices that manufacturers must follow, but rather provides a framework that device manufacturers must use when developing and implementing design controls.

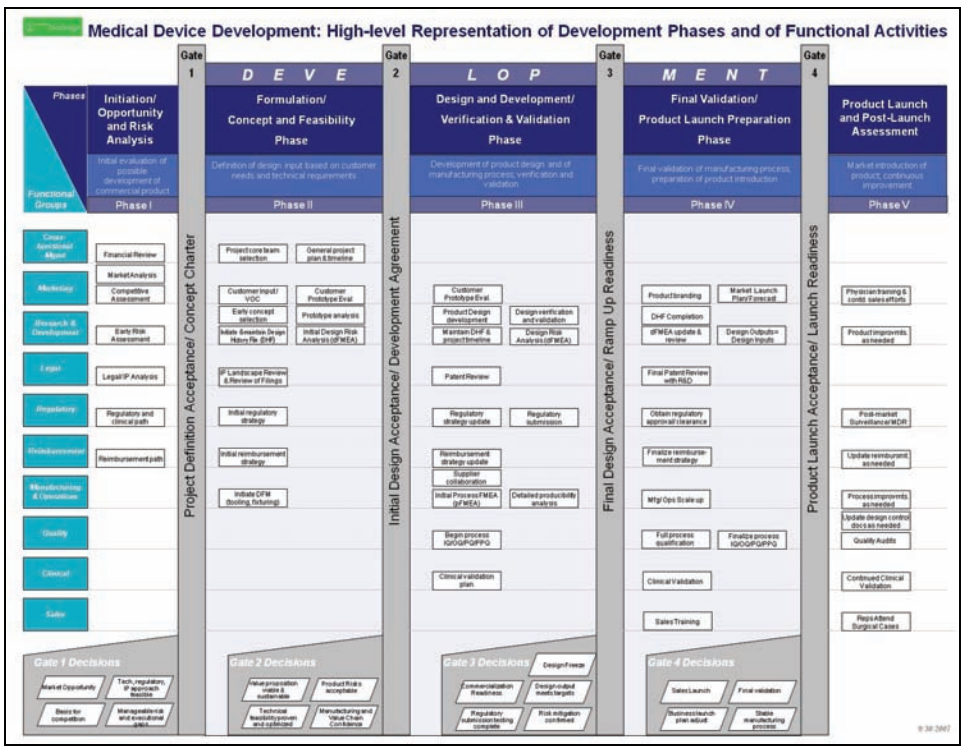

Figure 2. Linear Medical Device Development Model [1,3]

3.2 Variations to the Medical Device Development Model - Iterations Across Development Phases

The presented product development model (shown in Figure 2), as noted in the beginning, illustrates the device development process in a linear form in which development smoothly transitions from concept to final launch without disruption. However, due to the many challenges and complexities associated with medical device design and development, a smooth development path rarely occurs. Design teams within medical device companies often encounter roadblocks along the path from concept to launch, and into post-market surveillance. This section illustrates examples of some of the iterative development loops that frequently occur along the development pathway. The iterations presented are based on responses from the device experts interviewed in this study, and should be regarded as an extension of the linear model. Figure 3 provides an upper-level view of iterative loops *across development phases*. A closer examination of several across-phase iterations are then presented in Figures 4 though 11, with a corresponding description of each.

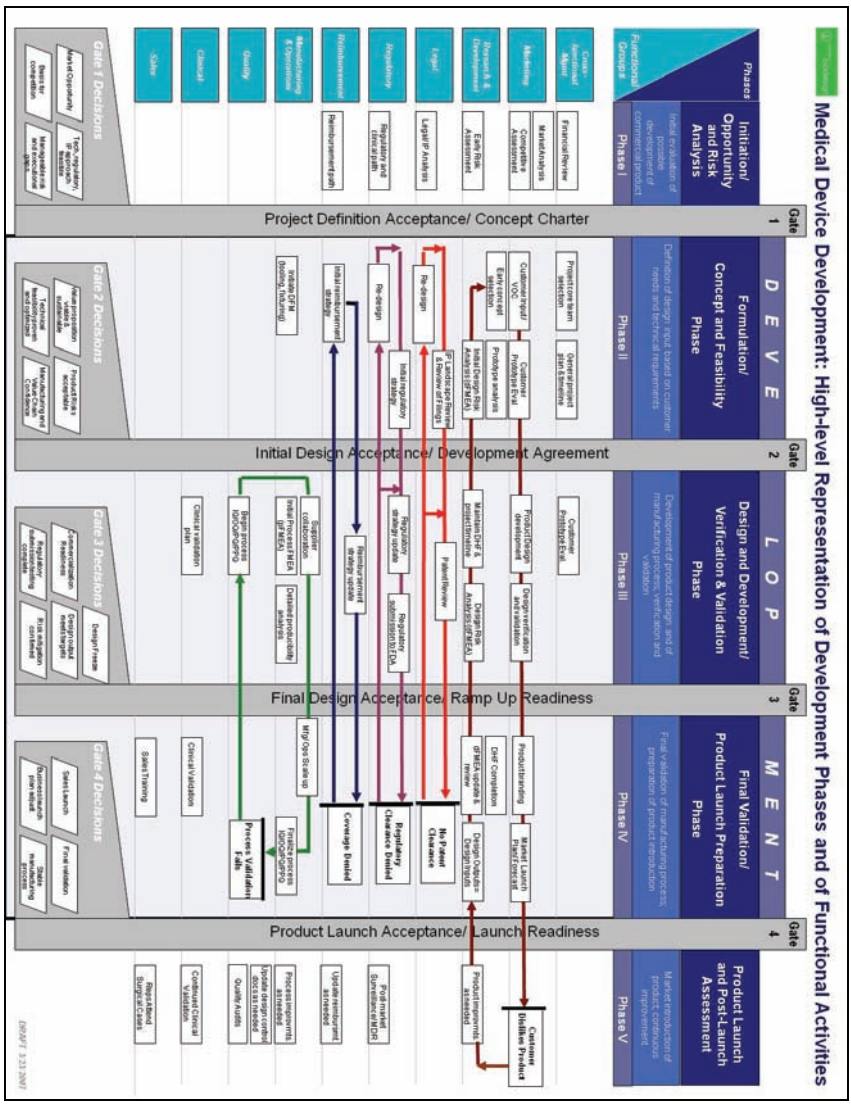

Figure 3. Variations to Linear Device Model: Iterative Loops Across Development Phases

User (Physician) Feedback

As illustrated in Figure 4 below, the iterative design process in the medical technology industry may be repeated several times until the device's user needs and functionality requirements are fully satisfied. A device concept is typically generated in Phase 2 of development in order to address a specific clinical need. Then, in Phase 3, a functional prototype is often created and presented to device users (i.e. physicians and nurses) in order to obtain user feedback. Based on the feedback received, the design is then modified accordingly. The loop may be repeated, often several times, until the needs of target users are fully met.

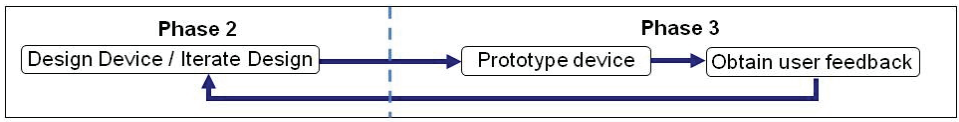

Figure 4. User Feedback Loop

As an example, the ZONARE Z.one Ultrasound Imaging System case study illustrated that dynamic course-corrections based on user feedback along the technology development pathway were critical to the company's success. After presenting their initial prototypes to device users and obtaining widespread market feedback, it became clear to the company that most doctors perceived their product's handheld transducer to be too bulky and too heavy, and that the screen size was too small. As a result, the product's design was reconsidered and underwent multiple prototype iterations. This case also highlighted the need to obtain feedback from future users in various settings of care, as opposed to just industry thought leaders, in order to obtain unbiased feedback that reflects a more realistic market response.

Product Pre-Validation (Performance) Testing

Once a functional or working prototype of a device has been constructed in Phase 2 of development, a device will often undergo bench top and/or animal testing to prove technical feasibility (Figure 5). Bench top testing involves constructing a physical model to assess design performance. Pre-clinical testing involves selecting an animal model which most accurately represents the area of the human anatomy in which the final product will operate. Animal studies are often used to better understand how the device will operate *in vivo*. If the results of either bench top or animal testing produce a negative or unexpected outcome, a design failure modes and effects analysis (dFMEA) is often evaluated, and the device may be re-designed and subsequently re-tested. This pre-validation testing loop may occur several times during the process of device development. In certain instances, a product development project may be terminated if it repeatedly fails to transition to the next development phase.

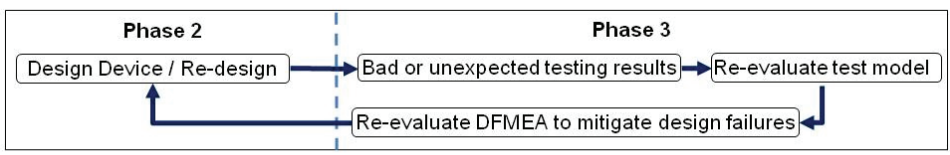

Figure 5. Performance Testing Loop

Product Verification & Validation Testing

Once a device is designed and prototyped in Phase 2, the device may undergo pre-validation feasibility testing. Following design freeze in Phase 3, formal Verification & Validation (V&V) testing begins (Figure 6). Test failure may occur during Phase 4 of development if the device does not properly indicate that design inputs have been met and/or that user needs have been satisfied. If V&V test failure occurs, engineers will examine the test results and determine the root causes of failure. Design changes may then be implemented as needed, and the V&V test cycle repeated based on the modified design. It should be noted that if testing failure were to occur during the pre-validation testing phase, then a re-design would occur sooner in the development cycle.

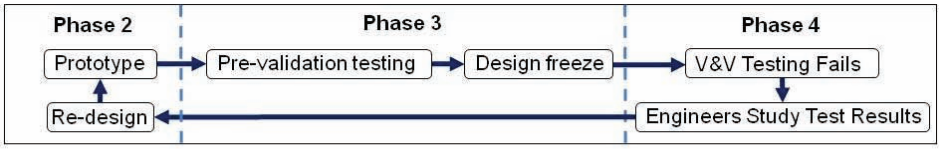

Figure 6. Verification &Validation Testing Loop

Boston Scientific (formerly Guidant's) Contak CRT-D cardiac resynchronization therapy case illustrated the magnitude and scope of testing that companies can perform both pre-clinically and clinically, and the emphasis both the device industry and FDA place on product safety. However, despite comprehensive testing efforts, the case also provided evidence that an ultimate guarantee of safety is not always possible. The Guidant ICD recalls that have been widely discussed in the industry and in public (with the CONTAK CRT-D system being one of the affected technologies), revealed the need for continued efforts by regulatory agencies, manufacturers, and practitioners to increase device monitoring so as to detect as early as possible any signals that could evidence potential device malfunction.

Intellectual Property

Once a design concept has been generated and intellectual property has been filed, it is necessary for a product development team to continue monitoring its patent portfolio. Routine patent surveillance ensures that a company will have freedom to operate (FTO) at the time of product launch. Likewise, as the design evolves, it is necessary to ensure that new design features do not infringe upon existing patents. If FTO is denied by the team's patent counsel (Figure 7), then a product re-design must occur. A design's final launch is contingent upon receiving clearance from the company's patent counsel.

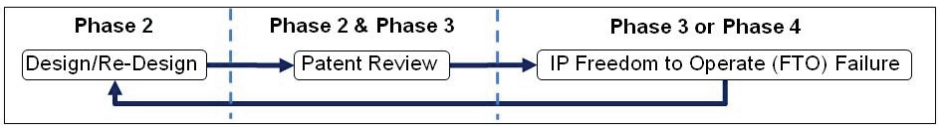

Figure 7. Intellectual Property Loop

Process Validation & Manufacturing

A device can undergo a process validation loop, as is shown in Figure 8. The IQ/OQ/PQ/PPQ[2] process typically begins in Phase 3 of development, per the linear model. If the process validation fails, perhaps for instance, because a process was more sensitive to parameters than had been originally anticipated, the root cause of failure will be identified, and the process will be changed. The process validation is then performed a second time and the loop repeats itself; thereby increasing the product's overall development time. If the process validation passes, parts will subsequently be manufactured.

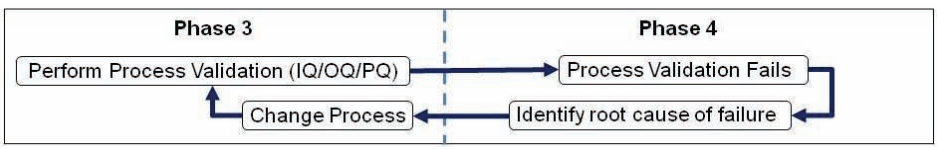

Figure 8. Process Validation (IQ/OQ/PQ) Loop

The Edwards Lifesciences FloTrac Sensor case study presented an alternative example in which its manufacturing process was expedited in order to shorten its product development timeline. While almost all FloTrac Sensor development was handled by Edwards in-house, collaboration with Analogic, the maker of the monitor hardware, was crucial, since the two companies were able to

[2] IQ=Installation Qualification; OQ=Operational qualification; PQ=Performance Qualification; PPQ=Product Performance Qualification

leverage their joint experience from previous joint development activities, to expedite product manufacturing.

Regulatory

As has been shown in the general development model, once a design is established and V&V testing and clinical trials (if needed) are completed, a submission is made to the FDA to obtain regulatory approval[3] for the given device (Figure 9). It is common for the FDA to respond to a company's regulatory submission with questions regarding test results and test methodology. When this occurs, additional testing is often performed in response to the FDA's inquiry. The FDA will then either deny or grant approval, or conditionally grant approval with the request for further testing. If regulatory approval is denied, a re-design may be required. In the worse case, FDA approval will be denied immediately following submission, without questioning, and a complete re-design may be required immediately.

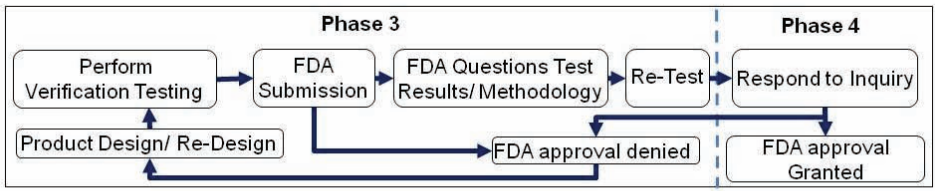

Figure 9. Regulatory Iterative Loop

Genomic Health's Oncotype DX Breast Cancer Assay exemplified an interesting variation to the linear development model, from a regulatory perspective. The Oncotype DX assay is one of the first proven tests that fall under the scope of what has been referred to as "personalized medicine." The company's in-vitro multivariate assay (IVDMIA) represents a new generation of technologies that are not currently regulated by FDA's Office of In-Vitro Diagnostics (OIVD). Genomic Health maintained that its Oncotype DX test is a clinical laboratory service that is not subject to FDA regulation, but rather to CLIA regulations (Clinical Laboratory Improvement Amendments of 1988). These types of personalized medicine tests will likely play a significant role in the future of health care, and thus begin to receive increased attention by regulators, payers, doctors, and patients.

Clinical Trials

A clinical trial feedback loop (Figure 10) can occur when a device exhibits performance issues either during pre-market trials (in Phase 3) or during post-market surveillance trials (in Phase 5). Once feedback regarding device performance is received from a field CRA (clinical research associate) this feedback may then be relayed to clinical management. Clinical management may then notify the product's marketing manager who then relays the information to the R&D engineers responsible for device design. For smaller companies with fewer roles and functional groups, feedback from the field may be relayed directly to R&D. If a design problem occurs during clinical trials, the device may need to undergo either design modifications or a complete re-design. If a design flaw is detected following market release, depending on the severity of the issue, the device may need to either be recalled or possibly enhanced in some way to satisfy the needs of a specific physician customer. Both scenarios present problems that can lead to severe ramifications and product delays, e.g. caused by new clinical protocols required to continue testing.

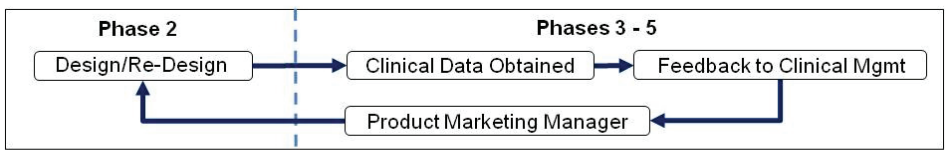

Figure 10. Clinical Trial Feedback Loop

[3] For the remainder of this chapter, the term "approval" is used for simplification instead of "clearance / approval." 510(k) submissions are cleared, PMAs are approved by the FDA.

In some instances, as evidenced by the GuardWire® Temporary Occlusion and Aspiration System case study, a clinical trial will be conducted for marketing purposes following initial regulatory approval, in order to lift labeling restrictions and expand a product's indications for use. PercuSurge was successful in obtaining its initial 510(k) regulatory clearance by demonstrating substantial equivalence to two devices that were quite different from the GuardWire (one non-catheter-based occlusion device and a regular catheter). However, the labeling indications required by the FDA for use were quite limiting relative to the intended market. As a result, PercuSurge conducted a clinical trial (referred to as the SAFER trial) and sought an additional 510(k) clearance for extended indications.

Reimbursement

Based on interview responses and the FloTrac Sensor case study, reimbursement was shown to have one of the greatest impacts on device development, from a monetary and market adoption perspective. Although reimbursement strategies are typically initiated in the earliest stages of medical device development (per the linear model), the decline of widespread approval by private and public payers in the later stages of development can present a major set-back for developers.

The FloTrac Sensor case study illustrated a case in which a company strategically updated its reimbursement plan to appeal to a broader market. Edwards Lifesciences made the difficult decision to postpone the sensor's final hardware design choice until later in the development process, in part, to appeal to the divergent markets the company intended to approach. That is, while the US and European markets supported the concept of disposable sensors in their reimbursement scheme, the Japanese reimbursement landscape was significantly different, and this required additional considerations for product design. The reason for these differences was the anticipation that reimbursement in Japan would possibly need to be based on a reusable sensor concept, requiring different design features than the disposable. Because of the ambiguity about the most promising reimbursement strategy for the Japanese market, Edwards continued parallel development of its disposable and reusable sensor, even as the design choice for the device was finalized for the European and United States markets.

Limited Market Release (Beta Launch)

During a limited market release (or so called "Beta Launch") in Phase 5, a device can either be accepted or rejected by a select group of physicians who have been chosen to evaluate the technology (Figure 11). If the device is accepted by the select user group, then the company will proceed to a full launch. However, if the design is rejected by physicians in the Beta Launch, the device will likely be re-designed and re-tested, requiring returns to earlier development activities.

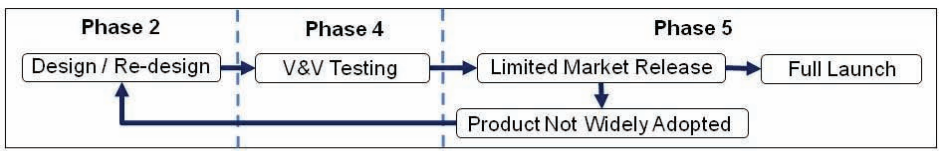

Figure 11. Limited Market Release (Beta Launch) Design Loop

3.3 Development Variations for Drug/Device Combination Medical Products

In light of the medical device development model presented earlier, the innovation cycles and development of combination medical products (which consist of device/drug/biologic combinations), presents several unique model variations. Examples of combination medical products include drug-eluting stents, antimicrobial or heparin-coated catheters, pacing leads with steroid-coated tip, anti-infective sutures, and orthopedic implants with growth factors [5].

Combination product development is largely influenced by differences in innovation cycles between pharmaceuticals and medical devices. Pharmaceutical innovation cycles occur every ten to twenty years, whereas devices can become obsolete within a period of months. Thus, in order to produce new products on a more frequent basis, combination product manufacturers may choose to innovate through developing new device delivery systems that are compatible with existing drug therapies.

However, robust material testing and a complete evaluation of device/pharma interactions must occur for every device iteration.
Combination products experience unique innovation challenges in terms of a physician's involvement with development. For devices, a physician will often identify a clinical need, and then a device is built to satisfy that need, as was discussed earlier. However, for products involving pharmaceuticals, physicians largely rely on drug companies for information on new drugs and novel excipients. Thus pharmaceutical research largely drives the drug component of combination products, whereas clinical needs drive the device component.
The development of combination products is distinct in that it requires integrating the knowledge base of several disciplines (i.e. biology, chemistry and engineering), each of which rely on specific terminology and design methodologies. Consequently, companies developing combination products must establish a team structure that is dissimilar from either traditional pharma or medical device development [6]. For example, in addition to the functional areas presented in the linear medical device development model, combination product development often requires an additional R&D analytical testing group. Also, supplier quality is typically a separate group in combination product development, distinct from the manufacturing and operations groups in traditional device development. Merging teams of individuals from pharmaceutical and device development requires increased discipline and cross-functional coordination.
Combination product development demands a smooth integration of design practices traditionally used for device development with processes used specifically for pharmaceutical development [7]. As is shown in Figure 12, prior to Phase 1 of the linear medical device development model, a drug and its dosing and coating requirements are typically established. Parallel efforts are underway prior to Phase 1 on the device side to explore existing device delivery systems and perform material tests to ensure there will be no unexpected drug/device interactions during the integrated stages of product development. Thus, by the start of Phase 1 the drug risk has been mitigated for the development of combination products, and early R&D process development begins.
On, the financial front, combination product development often produces higher returns than do traditional medical devices. Yet, development tends to be riskier, incurs higher costs, and often requires longer timelines [7].

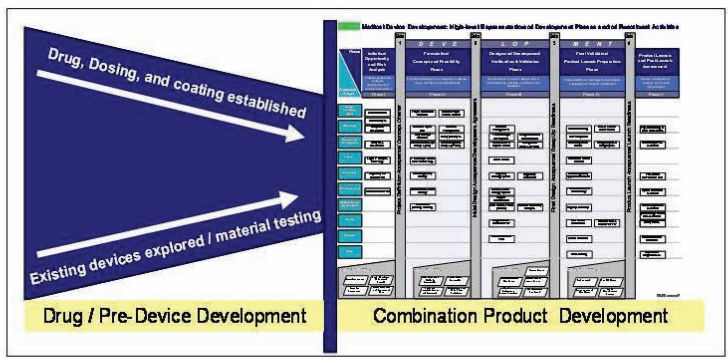

Figure 12. Schematic of combination product development

3.4 Medical Device Development Variations Influenced by Financing

Many aspects of the medical device development process are substantially influenced by the availability – or lack of – sufficient funding. Recruiting of a strong development team or pursuing a series of sufficiently large clinical studies in a timely manner are typical examples, among many, of how the process is shaped and altered by funding constraints. The same holds for timely and optimal access to other, non-financial, resources, which are frequently offered by so-called technology incubators [8].
Large medical device companies often categorize device development efforts by investment type. For instance, external opportunities are those in which the product portfolio is expanded through acquisition. Whereas, internal opportunities are those in which in-house development efforts occur.

Joint development efforts are those that involve working with other companies to bring a new product to market. For each, concept creation differs during Phases 1 and 2 of development, yet product development efforts are quite similar during the later stages of development (Phases 3 to 5).
For medical device start-ups, a close relationship tends to exist between reaching development milestones and managing to raise new capital. The reason for this relationship is two-fold. On the one hand, investors perceive the risk of a technology to be significantly lower after certain milestones have been reached (e.g., first-in-man studies), making it easier for them to allocate funds [9]. On the other hand, companies have often exhausted their capital to reach these milestones, and thus need new funding to fuel further development and commercialization efforts. It should also be noted that the exit strategy for a new medical device venture, which is closely related to the type of funding received, can have a distinct impact on the development strategy, e.g. the indications sought with a therapy, or the outreach to an international market in addition to the domestic market [10].

4 DISCUSSION

This paper illustrates that medical device development can be a highly iterative and non-linear process. The linear model prescribed by the FDA and followed by companies across most innovation settings presents an ideal case for device development. Though the linear model provides a clear and comprehensive representation of device development, the data illustrates that this model should be followed with an understanding that the development process may involve unexpected challenges and non-linear iterations.
Through in-depth interviews and case studies, the InHealth research study revealed a variety of iterative loops and model variations that may occur across development phases. The across-phase iterations highlighted in this paper include: user feedback loops, pre-validation testing loops, verification & validation test iterations, intellectual property iterations, process validation and manufacturing loops, regulatory and clinical trial loops, and limited market release iterations.
Variations to the linear device development model were also shown for combination medical products, due to their unique innovation cycles and the requirement for functional groups that do not typically exist in traditional med-tech development teams. Development variations that are heavily influenced by financing in the medical device industry were likewise presented. Med-tech incubators, large medical device companies, and start-ups were each shown to follow development patterns that are somewhat unique to their method of financing.
In conclusion, experts in the medical device industry are in wide agreement that advances in medical technology will fundamentally transform health care and delivery systems in the next decade, and that it is imperative for safe and effective technologies to be brought to market in the most streamlined and accelerated manner. In May 2006, the FDA's Medical Device Innovation Initative announced that it will "need to ensure that clinical trials, product reviews and approvals, and manufacturing processes are conducted in the most efficient and effective ways" [11]. The outcomes of the InHealth study, and process variations presented in this paper, reveal that new models may be needed which adhere to QSR guidelines, while capturing the highly complex and iterative nature of medical device design. An accurate understanding of the challenges inherent to device development in the med-tech industry could be used by designers, developers, policy makers and regulatory agencies to guide realistic development programs and to promote the efficient advancement of new and complex medical products.

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