A NOVEL APPROACH TO BUSINESS PROCESS DESIGN IN

A REGULATED INDUSTRY

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In A Regulated Industry

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Today, medical device companies need to be compliant to global regulatory requirements and at the same time, streamline and shorten their product development lifecycle so they can secure the competitive advantages that come from being first to market. That means improving efficiency throughout the product development process, from development through regulatory approvals (around the world), while remaining compliant during all phases of the development. Required product development efforts, however, are constrained by the global regulations and are challenging efficiency throughout the Product Development process. Consequently, there is a recognized and critical need to know and manage this global regulatory knowledge in a way that will ensure global compliance yet also optimize product development activities. In an increasingly global market, filtering through the various distinct country regulations, global directives, standards, national legislation, mandates and guidelines necessary to develop product and ultimately secure regulatory approval can seem to be an insurmountable task. Yet, due to the expansion of global markets and the marketing

opportunities that result, understanding and managing the global regulations is more important than ever. Therefore, there is an unfulfilled need to develop a theoretical process to manage these large volumes of information, and a methodology which can be used to manage this huge, diverse and changing knowledge base. This can ultimately contribute to a more efficient product development process while maintaining global compliance.

Without doubt, however, managing this knowledge, communicating this knowledge, and using this knowledge in a way that can also optimize product development efforts is a real challenge. Recognizing the need to operate in a way that meets both the business needs as well as global regulatory requirements is driving medical device companies to design and develop systems or tools to address the challenges of managing regulatory knowledge and subsequent compliance throughout the product development process. Designing these systems or tools to manage compliance knowledge, however, is not typically done using true design methodologies that provide some structure and a systematic approach to its design.

Axiomatic Design for Business Process (ADBP) provides this type of an approach to designing a solution capable of meeting all the stakeholders needs. Based on the known Axiomatic Design Methodology, it is a new and significant technique or design methodology for developing a business process in the regulated industry. The methodology utilizes customer needs as input and produces operational requirements, instructional requirements, and deliverables through the use of matrix methods.
This theoretical approach to designing methodologies to manage regulatory knowledge is a superior approach to designing the most efficient and compliant framework in the

regulated medical device industry that improves efficiency throughout the product development process, from development through global regulatory approvals, while inherently and efficiently remaining compliant during all phases of the development and as well as consistently demonstrating “safety and effectiveness”.

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AD – Axiomatic Design

ADBP- Axiomatic Design for Business Process

AIMD – Active Implantable Medical Device

PDLC – Product Development Lifecycle

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Chapter 1

INTRODUCTION

Today, medical device companies need to be compliant to global regulatory requirements and at the same time, streamline and shorten their product development lifecycle so they can secure the competitive advantages that come from being first to market. That means improving efficiency throughout the product development lifecycle, from development through regulatory approvals (around the world), while remaining compliant during all phases of the development. Required product development efforts, however, are constrained by the global regulations and are challenging efficiency throughout the Product Development lifecycle. Consequently, there is a recognized and critical need to know and manage this global regulatory knowledge in a way that will ensure global compliance yet also optimize product development activities. In an increasingly global market, filtering through the various distinct country regulations, global directives, standards, national legislation, mandates and guidelines necessary to develop product and ultimately secure regulatory approval can seem to be an insurmountable task. Yet, due to the expansion of global markets and the marketing opportunities that result, understanding and managing the global regulations is more important than ever.

Many companies tend to look at regulatory compliance as a sort of necessary evil that ultimately challenges efficiency throughout the product development process. Disaster in the case of noncompliance may result in loss of product certification, no regulatory approval, inability to sell the device, or worse yet, harm to a patient. Without doubt, however, managing this knowledge, communicating this knowledge, and using this knowledge in a way that can also optimize product development efforts is difficult. There is a real challenge, then, to striking the balance between compliance and pushing product through the pipeline in a way that secures that first-to-market competitive advantage.

Recognizing the need to operate in a way that meets both the business needs as well as global regulatory requirements is driving medical device companies to design and develop systems or tools to address the challenges of balance. Designing systems or processes to manage compliance knowledge throughout the product development lifecycle, however, is not typically done using true design methodologies that provide some structure and a systematic approach to its design.

Therefore there is a real design challenge and an unfulfilled need to develop a methodology which can be used to develop a theoretical process that can manage these large volumes of diverse and changing compliance requirements and operate in a way that can also *optimize* product development efforts.

Axiomatic Design (AD) is a system based design methodology. The formalities of the Axiomatic Design (AD) process could represent a potential solution to the design

problem. However classical AD has some limitations with respect to these regulated industries.

This research will first develop a system-based design methodology to be used for developing business processes in the global regulated industry. Next, this research will use this methodology to develop the specific design of a business process related to regulatory compliance efforts. Finally, this research will validate this design solution as an optimized approach for the regulated biomedical device industry.

This research intends to extend and formalize the Axiomatic Design (AD) methodology as a basis for providing structure and a systematic approach to the design of a business process, hence eliminating the present limitation with Axiomatic Design in this environment. The Axiomatic Design method, in this research, would be expanded to cover the business processes as it applies to regulated industries. There are sure to be some challenges with this that will expand the rules of axiomatic design. For example, Suh describes the design world to include four domains that create demarcation lines between the four different design activities. (Suh, May 2001) The product development process in the regulated medical device industry, however, is unique from other development processes in that it must incorporate "regulatory tolerance" for the changing global regulatory 'interpretations' and 'expectations'. "Regulatory Tolerance" is specifically defined by this author as "a variable regulatory expectation, interpretation, or guidance, in an individual country or group of countries, based on the current regulatory environment of that country". Therefore, there will be a need to adapt and expand the AD methodology for this type of industry. Likewise, there will be the need to expand the

rules of AD as it applies to developing the recommended uncoupled design as a process design solution. Finally, there will be the need to develop an operational strategy or framework for this type of design solution. This framework can be used to enhance compliance required in the development of a medical device and optimize compliance efforts associated with the product development lifecycle, hence providing the extra time for innovation.

Chapter 2

BACKGROUND

There are two things driving biomedical companies today to become more operationally efficient: the rapid pace of global competition and an increasingly strict regulatory environment (MatrixOne, Nov 2003). As an organization and its customer base expand, the organization's focus tends to shift from end users and their requirements to the company's internal stakeholders and business operations or processes [also known as the Quality System] with operational efficiency becoming one of management's chief concerns (Mello, 2002). In the global biomedical device industry, this optimized efficiency must occur under the constraints of world-wide government regulations and the changing country expectations for both operational process and product requirements.

In the medical device industry, minimum operational regulatory requirements are defined, in part, in the process regulations such as ISO 13485:2003 and the US FDA 21 CFR (FDA) part 820. These regulations place great emphasis on the use of processes and procedures to regulate and control how internal business operations should be performed. In fact, the Code of Federal Regulations part 820 specifically mandates that "Each Manufacturer shall establish and maintain a quality system [business] process that is appropriate for the specific medical devices designed or manufactured, and that meets the requirements of this part" (FDA). Furthermore, in June, 1997, it was mandated by the

US FDA that in the biomedical industry, a detailed design control [also sometimes known as product development] business process be included as part of the quality system regulations (QSR) for certain classes of medical devices." (Teixeira, 2003)

Historically, the international and domestic medical device quality system regulations (QSR) were harmonized to have twenty elements to which the regulating bodies required compliance. Therefore, organizations typically had twenty procedures, all individually written to deliver compliance to a specific element of the regulations expected to define the business operations of the organization, and all too often only a pure regurgitation of the regulation content, not considering the collective needs of all stakeholders. This may have produced a 'compliant' procedure that in practice could neither consistently and repeatedly meet the requirements of the regulations nor provide stakeholder satisfaction. In the US, the QSR constitutes the FDA's expectations. It did not take into consideration the specific needs of the company. So when procedures were developed as a regurgitation of the regulations, companies may not have had the most optimized business process. What was seen is that even if the procedures were intended to produce written compliance, what often happened was the stakeholders meant to follow these procedures developed internal "work-arounds" to get to required deliverables or to avoid procedural tasks the stakeholders find non value-added. This now uncontrolled, unrepeatable process led to increased compliance risk [noncompliance] resulting in interrupted production and distribution, product liability exposure and delayed product approvals. From the compliance perspective alone, the US FDA recognized this. Surveys they conducted showed that although medical device

manufacturers have defined procedures, 30% still have problems meeting the regulatory requirements (Teixeira, 2003). Likewise, there was also resource drains across the organization associated with addressing noncompliance: completing audit corrective actions, repeating procedural tasks, re-test, re-work, and writing revisions to the procedures. This, in part, has been due to companies establishing procedures and not a business (or quality system) process that fully understands the stakeholders requirements.

Then in 2003, regulatory requirements around business processes changed with the revision of the International Organization for Standardization's Quality System regulation, ISO 13485:2003. This required biomedical device industries to look at their business operations from a process perspective as opposed to the procedural element approach. While the United States did not adopt this approach, most of the rest of the world did and does today. Regardless, one thing remains true whether domestic or international, government enforcement of the regulations is increasing and regulatory agencies are expecting more of biomedical device manufacturers in terms of process efficiency and cross-functional process definition. This is driving organizations to improve their processes in order to meet new regulations and expedite development in the interest of the public health, while still fulfilling their obligation to develop safe and effective products.

As regulatory agencies are recognizing the need for engineered product solutions that can be trusted, the business processes by which these products are created must be reliable, optimized, and robust. This has to be achieved by being well thought through and meeting the requirements of all the stakeholders that define the system. So

companies are faced with redesigning how they operate from a more systematic and comprehensive manner under the constraints, expectations, and increasing demands of the regulating bodies.

2.1. Problems/Challenges

In the biomedical industry, innovation is key. But you can't have innovation without safety, effectiveness and regulatory compliance. And you can't always comply and get to market as quickly and affordably as you'd like. Many companies tend to look at regulatory compliance as a sort of necessary evil that ultimately challenges efficiency throughout the product development process. Yet disaster, in the case of noncompliance, may result in loss of product certification, no regulatory approval, inability to sell the device, or worse yet, harm to a patient. There is a real challenge, then, to striking the balance between compliance and pushing product through the pipeline in a way that secures the competitive advantage of being first to market.

The problem is that the business (quality system) procedures that are responsible for defining the operations surrounding designing, developing, building, and selling this innovative product have typically been only regulation driven, leading to significant inefficiencies resulting in unsatisfactory business operations, slower times to market, poorer product quality, and increased costs. The regulations, however, are only part of the requirements for an optimal business 'process'.

Another and arguably more significant part in this effort is understanding and incorporating the requirements for the business operations from *all* of the stakeholders

involved in that process, including the implementers of the process as well as the global regulators. Typically, there are few processes developed using true design methodologies that provide some structure and a systematic approach to its development. Business, or quality system, processes are not typically designed with the same robustness with which the product is designed. It is meeting the totality of the stakeholder requirements within the process that ultimately yields quality. Yet still, I have seen that the paradigm is hard to shift and process design becomes an exercise in subjective opinion and such other types of ephemeral "tools" from when processes, or more so the procedures that define the process, were defined in a vacuum and primarily to meet regulations. So business (quality system) processes are still often designed without consideration of all stakeholders.

Business processes cannot be created in a vacuum and one size does not fit all. So each manufacturer has the responsibility to establish requirements for the type of product they develop, the countries in which they intend to sell their product, and the people who will be implementing the process. Additionally, they must determine the most value-added operational concept or framework that can implement these processes.

In the governing biomedical Directives, there are required standards that govern process such as Risk Management and those that govern product testing and development, such as Safety standards. Often, there is no dedicated resource to define, interpret, and educate the division in a consistent and accurate way on which product standards, clauses, test criteria, etc. are applicable for the specific technology, from around the world. This may be left up to the working engineers on the project team.

Hence, engineers typically work to comply with these standards in a project by project approach. This increases the adverse potential for complexity, inconsistency, inaccuracy and inefficiency in process and documentation, such as; with requirements management, verification test definitions, protocol development, and regulatory measures for each project of the same product type. They may take a best guess at which product regulations are applicable to the technology being developed, based on a past effort, and usually only as it relates to the United States and the European Union. Many times, the project teams don't find out until either late in the development cycle (after a regulatory submission rejection) or after not being able to sell into a country, which standards and/or national legislations are applicable, or more critically, what the current interpretation and expectation is of the standard requirements. This operational strategy delays the product development lifecycle due to redundant paperwork activities, rework, and redesign and increases regulatory risk to the organization, by creating complicated, variant documentation and a lack of apparent compliance to the technical product standards.

Complicating the situation is that product and process standards are influenced by a current regulatory environment and specific country interpretation or expectations of the standards and regulations that drive the needs and requirements for these types of business processes and product requirements. For example, in the case of a medical device with a radio component, globally many countries might mandate the use of ETSI EN 301 839, Electromagnetic Compatibility and Radio Spectrum Matters (ERM); Radio Equipment in the Frequency Range 402 MHz to 405 MHz for Ultra Low Power Active Medical Implants and Accessories. This is a constraint. Yet, even though a company

designs and tests under the constraint of the standard, a specific country may wish for, or expects, verification testing to be done in their own country or by a designated lab. This is done, for example, in some Asian countries. This is not a constraint of the standard itself, rather an expectation of that country based on the current regulatory environment.

Furthermore, the implementation of regulations and standards in the biomedical device industry has become more risk based, which is widely open to interpretation. So some regulatory requirements might constrain what functions have to be considered in a business operation or process for the regulated industry, but they do not constrain *how* to do this, whereas the "regulatory tolerance" might. In the same way, there are global product standards that can influence the product development business process. These requirements are to the process, as product requirements are to the product they produce. More complicated technology, requiring greater cross-functional involvement and more demanding stakeholder needs, leads to more complex process solutions that result in safe and effective products being developed and manufactured. These types of operational efforts are also challenged by the changing global directives, standards, and national legislation and, in turn, are challenging efficiency throughout the product development lifecycle.

Herein lays the challenge of balancing process that pushes product through the pipeline and at the same time, meeting all stakeholder and compliance requirements. The Product Development, or Design Control, process is the business process biomedical manufacturers most often try to optimize and continuously improve, not only in an effort to meet the changing demands of regulating bodies, but to meet more demanding

stakeholder needs, including the regulators. Likewise, there are more challenges with competition. In effect, companies need to reduce time to market, increase product quality, ensure organizational compliance, and decrease development costs. So the design of a business process that optimizes efforts throughout the Product Development Lifecycle can largely lead to the medical device manufacturer's success or failure.

2.2. Research Needs

For many required product development activities the process driving compliance to global regulations *can* be constraining when operationally applied project by project, as is typically the case. That being said, the processes that manage compliance requirements and use these requirements in a way that can also *optimize* business and product development efforts is a real challenge. While there are many tools to help companies manage the resulting deliverables of compliance activities – essential requirements checklists, tracing, etc. - there is still a recognized and critical need to develop a 'process' or system of activities that will manage the global regulatory compliance efforts in a way that will ensure global compliance, optimize product development activities, and prevent disaster. Additionally, there is a need to develop an operational strategy for this type of process or system.

Therefore, medical device companies are faced with redesigning how they operate from a more systematic and comprehensive manner, operating in a way that meets both the business needs of the internal stakeholders as well as new demands and requirements of regulating bodies, thus driving companies to improve their business operating

processes or tools, as well as needing to develop the operational strategy or framework for implementing these processes.

While there are many less rigorous ways to design and develop a process, using a rigorous design methodology offered the type of innovative solution to this challenge that when implemented, offers a medical device organization a real competitive advantage.

There are many design methodologies that already exist and some build on the premise of others. One in particular provided the structure and a systematic approach to product development that was useful in addressing this design challenge. Axiomatic Design (AD) is this rigorous system design methodology that provides this type of approach to design. It uses matrix methods to systematically analyze the transformation of stakeholder needs into functional requirements, design parameters, and process variables. It integrates scientific principles and system engineering tools into the design process, in order to improve design activities. The formalities of the AD process could represent a potential solution to the design problem (Easton D. July 2007). However, it was determined that classical AD has some limitations with respect to these regulated industries, as well as other industries which have similar business processes (Easton D. , 2010).

There were challenges with using AD that expanded the rules of Axiomatic Design. For example, Suh describes the design world to include four domains that create demarcation lines between the four different design activities. The product development process in the regulated medical device industry, however, is unique from other development processes in that it must incorporate the "regulatory tolerance" for the

changing global regulatory interpretations and expectations. "Regulatory Tolerance" is a term introduced and defined by this author as "a variable regulatory expectation, interpretation, or guidance, in an individual country or group of countries, based on the current regulatory environment of that country".

The real goal of any overall design effort is to optimize the performance of the system (Hintersteiner, 2000). Consequently, there was an unfulfilled need to develop a design technique or methodology and subsequently a design solution for a "process" or system of activities, which surrounds regulatory compliance, where regulatory compliance is not just a deliverable of the product development process, but a driver to its optimization.

Therefore, there was a need to adapt and expand the AD methodology for this type of industry. As a result, there was also be the need to expand the rules of AD as it applies to developing an uncoupled design for a cross functional process. This systematic approach to translating, prioritizing, organizing, analyzing and decision making on design requirements is a superior tool in developing the simplest, most efficient and most compliant business process or system and operational framework, in the regulated biomedical industry.

2.3. Literature Review

There is endless research on optimizing the product development lifecycle. There is even extensive research of medical device development models, such as in the 2007 Study of Medical Device Development Models (Linehan, Pate-Cornell, & al, 2007).

This is useful information that supports the authors engineering judgment and will be used throughout this research. The focus of this research, however, is not just optimizing a product development lifecycle. It is doing so based on a novel rigorous design methodology and is specific to the regulatory compliance chain of events of a biomedical device organization. The literature that discusses optimization of product development in general is different in that most cases are theoretical, and most texts are not using the Axiomatic Design methodlogy as a basis for optimization. Therefore, the focus of the literature review was tailored to research using Axiomatic Design.

There has been a lot of research in the area of Axiomatic Design (AD), especially in the last decade. More recently, there has been research in ways to use AD in decoupling designs where there is inherent coupling. Research using AD in the bio medical or healthcare industry is definitely ramping up as trends in this industry often follow those trends from the Department of Defense or automotive industries, where research in AD has been applied for past years.

The website, www.axiomaticdesign.com has the largest database of research papers on Axiomatic Design. Likewise, since Nam Suh, originator of Axiomatic Design, was on the faculty at MIT previously, a large amount of research involving AD can be found at the following website, http://dspace.mit.edu/handle/1721.1/7582, which includes the full text of MIT theses and dissertations. And of course general internet searches were performed. Based on this literature review there is no evidence that Axiomatic Design has been modified into a novel technique to be used for developing disaster tolerant business processes in regulated biomedical industry.

When developing a product of any kind, it is critical to evaluate the needs of all of the customers. Likewise, it is wise to draw from trends in other industries. This sentiment is echoed by Michael Wiklund in his paper, Medical Device Design: Developing a Winning Strategy (Wiklund, 2005). Wiklund says that when developing medical devices, it is critical to take a structured design approach. Additionally, he expresses that if one draws on trends from other industries, people will already be familiar with the product to some extent. It is the opinion of the author that this should remain true when developing the processes and instructions used to design and build medical devices.

Lead times at each phase of the product development process are different and depend on the complexity of the product design, as well as the process or work instruction used to work through these phases. Shortening time at any stage along the lifecycle can result in a more timely product introduction; and simplifying the process may eliminate unfortunate re-design at a later stage. This is also being recognized in other industries such as construction. For example, Sohlenius and Johansson explain a framework for decision making when building houses in Sweden. In this, they attempt to address variation as is proposed in this research, however their focus is of interests over the long lead times required to construct buildings. The aim of their research is to use AD as their framework (Sohlenius & Johansson, 2002). My research used a modified and enhanced Axiomatic Design for Business Processes, to recognize the operational framework necessary to implement my design solution.

Others have recognized the benefit of applying a structured design approach to the design and development of processes, as does the author of this document. For example, Sohlenius, G, et al describe, in The Innovation Process and the Principle Importance of AD, a modified AD approach for the Industrial Innovation process. In this modification of AD, they suggest adding two additional axioms to AD principles to address energy and time. If energy and time are not already constraints, then once someone implements the basic AD methodology, they would analyze the design against the first two axioms, and if those are met, then analyze against the additional two axioms. The thought is that these two axioms will help to better address competency of those making the design decisions. (Sohlenius, Fagerstrom, & Kjellberg, 2002)

While there is the similarity of modifying AD to address a need, his approach is quite different from what this research proposes. First, the modification in Sohlenius' research is to address competency, not impact of various changing regulatory expectations. Second, this modification is an optional addition to the axioms of AD. The axioms may be applied, or they could be a constraint in which they would not be used as decision principles. (Sohlenius, Fagerstrom, & Kjellberg, 2002) In this research, the author changed design domains that result in an enhanced Axiomatic Design for Business Process and is not an option to Axiomatic Design itself.

Others are working to optimize design tasks at a more detailed level, where optimization is more typically carried out. Lee, et al writes about a Structural Optimization Methodology Using the Independence Axiom. This develops AD in a way where the design variables from the decomposition process are grouped according to

sensitivities. Then the sensitivities are evaluated by the Analysis of Variance (ANOVA) (Lee, Hong, & Park, 2009). Optimization is then quantified mathematically for the nearly uncoupled problem. In this research, the product is a tangible, not a process. Is suggests a method to analyze the data, not the method to obtain the data to be analyzed. It does not address the limitations of the design domains as this research did.

One of the more applicable pieces of literature in the body of knowledge is written by Qi Dong and Daniel Whitney, Designing a Requirement Driven Product Development Process (Dong & Whitney, 2001). This paper presents a technique to obtain a Design Structure Matrix from a Design Matrix enabling the reader to obtain design information flow patterns at an earlier stage in the product development process. The specific point of interest in this paper is the mathematical model used to validate the hypothesis. Future research could use a similar model as part of further research.

Below is a preliminary list of documents reviewed as part of this literature review. From this review it can be said that the concepts and proposed ideas for this research are novel and significant.

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Chapter 3

AXIOMATIC DESIGN (AD) AS A DESIGN TOOL

3.1. General AD Concepts and Existing Uses

Axiomatic Design (AD) is a system design methodology developed by Dr. Nam P. Suh at Massachusetts Institute of Technology (MIT) in the 1970's. He defines it as, "a system design methodology using matrix methods to systematically analyze the transformation of stakeholder needs into functional requirements, design parameters, and process variables. The method gets its name from its use of design principles or design Axioms governing the analysis and decision making process in developing high quality product or system designs." (Suh, May 2001)

The design concept has been used in the development of a variety of products and processes in many industries yet the definition of "design" depends on the field of interest in which it is being used. So "design" to a landscape architect may be in terms of ambiance for a yard, to a software developer may be in terms of design architecture, to a mechanical engineer may be in terms of a design product, to a manufacturing engineer may be in terms of a manufacturing process, to a business manager may be in terms of organizations and organizational goals, to a quality systems professional may be defined in terms of a quality system process. The point is, no matter the field of interest, there are

commonalities within these design activities to achieve the design goals. A single definition of design has been described by Nam P. Suh as "an interplay between what we want to achieve and how we want to achieve it" (Suh, May 2001). Commonly, designers have designed "iteratively, empirically, and intuitively, based on years of experience, cleverness, and creativity and involving much trial and error." (Suh, May 2001) Suh suggests that this isn't enough. Although very important, these factors alone are not sufficient in design and can result in costly and time consuming efforts that may not produce what the customer really desires.

AD is a science that has evolved from the technology of design. It infiltrates scientific principles into the design process in order to improve design activities. The argument and purpose for its use is to "augment a designers experience by providing the underlying principles, theories, and methodologies so that they can fully utilize their creativity" (Suh, May 2001). Ultimately, AD will "establish a scientific basis for design and improve design activities by providing the designer with a theoretical foundation based on logical and rational thought processes and tools." (Suh, May 2001)

As with any design methodology, the same steps are required: Understand customer needs; Define problem needed to be solved to meet needs; Create / select a solution; Analyze/optimize the proposed solution; Check design against the stakeholder needs. Progressing through these steps to determine the solution to the product design using AD is done through the following 5 items: domains in the design world, mapping between these domains, characterization of a design by a vector in each domain, decomposition of the characteristic vectors into hierarchies through a process of

zigzagging between the domains, and the design axioms - Independence & Information Axioms. (Suh, 1990)

Axiomatic Design has been used to design a variety of products and processes in many industries. However there is very little published about its use in the biomedical industry.

3.2. AD Domains

The fundamental concept of axiomatic design is that there are domains for each kind of design activity: customer domain, functional domain, physical domain, and process domain. The purpose is to use a decomposition process to translate requirements through each domain.

The customer domain is described by the needs (CNs) for which the customer is looking in a product or system. The functional domain is described by the transformation of the customer needs into a minimum set of specifications (Functional Requirements, FRs) that describes "what you want to achieve" to satisfy those customer needs. This domain also includes any constraints (C's) of the design solution. The physical domain describes the translation of functional requirements into design specifications (DP's) of the design solution that will satisfy those functional requirements. Finally is the process domain which characterizes the process variables (PV's) needed to produce the DP's. (Suh, May 2001)

3.3. AD: Mapping, Heirarchy, and Zigzagging

The decomposition process to transform the requirements into specifications between the domains is systematically analyzed using matrix methods. Design matrices are central to the application of Axiomatic Design. The design matrix begins with a systems perspective of the problem and cross references and maps the requirements from the top level of the system through each domain and system hierarchy ultimately indicating a coupled or uncoupled system. This alternating between pairs of domains to decompose design into hierarchies is called zigzagging. The hierarchies represent the design architecture and the decomposition process of requirements establishes hierarchies of FR, DP, and PV's.

As described in Suh's text, the mapping between the domains is represented by two design matrixes:

1. product design matrix, D, which shows the relationships between FRs and DPs, and can be summarized by: {FR} is the FR vector, {DP} is the DP vector, and [D] is the product design matrix - {FR} = [D] {DP}

$$\begin{Bmatrix} FR_1 \\ FR_2 \end{Bmatrix} = \begin{bmatrix} X & 0 \\ 0 & X \end{bmatrix} \begin{Bmatrix} DP_1 \\ DP_2 \end{Bmatrix}$$

Equation 1. Uncoupled Design Matrix.

$$\begin{Bmatrix} FR_1 \\ FR_2 \end{Bmatrix} = \begin{bmatrix} X & 0 \\ X & X \end{bmatrix} \begin{Bmatrix} DP_1 \\ DP_2 \end{Bmatrix}$$

Equation 2. Decoupled Design Matrix.

An X or O in a cell indicates whether the column's DP affects the row's FR or not and visually represents whether your design is uncoupled or decoupled. (Instead of a simple X or O, each cell can contain the mathematical relationship between the FR and the DP.) (Suh, Feb 1990)

3.4 AD: Design Axioms

Governing this analysis and decision making process for the best design solutions are design axioms. In fact, this is from where the method gets its name. Per Suh, there are two design axioms that were created by identifying the common elements present on all good designs. Once the common elements were identified, they were reduced to two axioms:

1) *Independence*: This axiom maintains and promotes the independence of various functional requirements, such that specific design parameters may be modified to satisfy a particular requirement without affecting other functional requirements.

2) *Information*: This axiom states that the information content of alternative designs should be minimized, thus maximizing the success of the design.

The AD process adheres to the two axioms through a rigorous dependence matrix formulation that uncouples (promotes independence) among the requirements. "When

there are two or more functional requirements, the design solution must be such that each one of the functional requirements can be satisfied without affecting the other functional requirements" (Suh, May 2001). The goal is to maintain the independence of FRs. In an acceptable design, the DPs and the FRs are related in such a way that a specific DP can be adjusted to satisfy its corresponding FR without affecting other FRs.

Designs which do not satisfy the Independence Axiom are called coupled. An everyday example is a typical water faucet. The two FRs are "control the temperature" and "control the flow rate." The two DPs are the hot- and cold-water handles. This design is coupled because it is impossible to adjust either DP without affecting the other FR: Each handle affects both temperature and flow rate. (Suh, May 2001)

Designs which satisfy the Independence Axiom are called uncoupled or decoupled. The difference is that in an uncoupled design, the DPs are totally independent, while with a decoupled design, at least one DP affects two or more FRs. Consequently, the order of adjusting the DPs in a decoupled design is important. In the above example, the two FRs- "control the temperature" and "control the flow rate" are independent. One DP does not affect the other so this design is uncoupled. (Suh, May 2001)

The purpose of the information axiom is to minimize the information content and thus select the best design among those that are acceptable. It states that "the design that has the smallest information content is the best design, as it requires the least amount of information to achieve the design goals." (Suh, May 2001). By avoiding complex functional requirements and focusing on simplified requirements with minimal information, the realization of a design adhering to the requirement is easier to achieve.

The goal is to minimize the information content: Among alternative designs which satisfy the axiom, the best has the minimum information content which means the maximum probability of success.

3.5 Axiomatic Design Limitations

The focus of the Business Process that is subject to this research surrounds regulatory compliance, where regulatory compliance is not just a deliverable of the product development process, but a driver to its optimization. Therefore the design solution for the "product" in this research is a design solution for a new "process". While there are many less rigorous ways to design and develop a process, using a design methodology such as axiomatic design offers the type of innovative solution to this challenge that when implemented, offer a medical device organization a real competitive advantage.

This research originally focused on the novel development of a design solution to satisfy the following question; "If we make an Active Implantable Medical Device (AIMD) that we want to sell globally, what kind of business processes do we need to develop to gain a competitive advantage in the future?" The solution must go beyond basic requirement management or tracing practices and must result in the reduction of risk and a cost return on investment. The intention was to apply Axiomatic Design to this challenge. There is no evidence this has ever been done to develop business processes surrounding Regulatory Compliance in a biomedical industry. However, once into implementation of the AD methodology, it was shortly recognized that the methodology

itself would have to be modified in order to adequately develop a Business Process around Regulatory Compliance that could be effectively used by a global company.

Based on the authors experience in the biomedical industry, it was determined that the breath of the process would need to satisfy customer requirements as described below:

CR1 A *simple* process that drives *efficiency*

CR2 A process that ensures global compliance for product technology

CR3 A Process that ensures global compliance for specific product

CR4 A process that supports entrance into the global market

CR5 A process that drives the "*right*" activities

Developing functional requirements, that will satisfy these customer requirements, must be done in a solution-neutral environment. To do this, one must rely on both a technical understanding of the global regulatory environment and global standards, and the knowledge of typical Product Develop operations of a medical device organization.

Applying this type of knowledge, understanding, and experience, and implementing a systems approach to satisfying the global customer needs resulted in the following functional requirements:

FR1 Systemize the approach for compliance requirements

FR2 Standardize the approach where possible

FR3 Customize the information for specific project

FR4 Deliver and maintain compliant products for regulatory approvals for new product, new geographies, new indications, changes to regulatory environment

FR5 Define, Capture, and Sustain a system for Global Regulatory Compliance Information for Product Approvals

The next step requires mapping Functional Requirements, in the Functional domain, to Design Parameters in the Physical Domain. At this time, it was recognized that using AD to design a Business Process in a regulated industry became “problematic”.

Chapter 4

AXIOMATIC DESIGN FOR BUSINESS PROCESSES (ADBP)

4.1 General

AD Advances and Applications, by Nam P Suh, states that AD may be used to create such designs as software, manufacturing processes, systems, or organization. As it is described today, applying the AD methodology to the design of a Business Process is complicated and confusing as the methodology is presently defined. As previously stated, while there are many less rigorous ways to design and develop a Business Process, using a design methodology such as Axiomatic Design offers the type of innovative solution to Business Process Design which may offer a biomedical device organization a real competitive advantage. But the confusion using the methodology as defined today lends itself to perceived complexity, the inability or more critically, the disinterest to use the methodology for the application of Business Process design, albeit the robust design approach and the axiomatic principles would be advantageous to designing an innovative Business Process.

While AD Advances and Applications provide examples using AD for a business/organization or a process (manufacturing), it does not for a Business Process. The text describes, for example, that the Process Variables in the Process domain for a

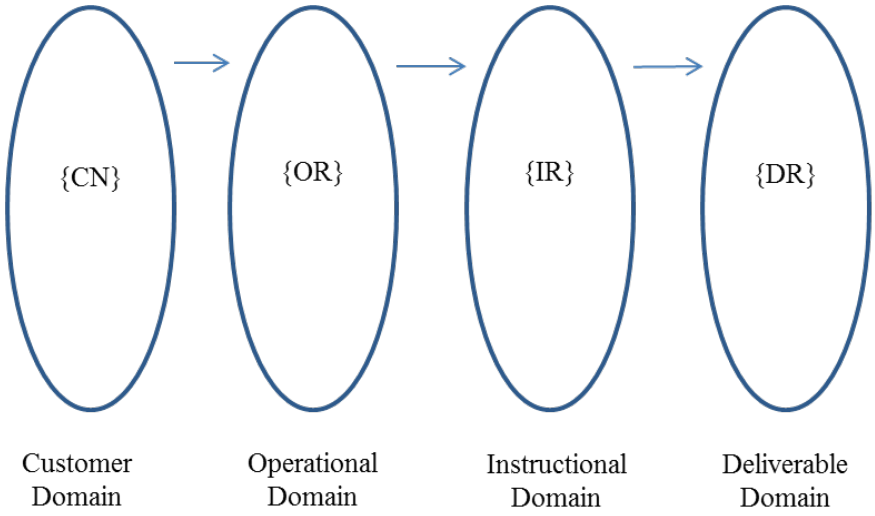
"business" might represent the human or financial resources. The Process Variables in the Process Domain for a manufacturing process might specify the manufacturing process variables that can produce the design parameter (Suh, May 2001). Neither of these is applicable to designing the "product" of a "Business Process" in a regulated industry. It becomes complicated and confusing, when trying to develop a total design solution for a Business Process, once one gets into the Process Domain. Therefore this research has introduced the required extensions, modifications and clarifications of the design methodology when developing a Business Process to solve the aforementioned problems.

A Business Process in a regulated industry should consist of procedures, instructions, and records or deliverables. Using a robust design methodology to determine the fundamental content at each level of the hierarchy certainly provided an option that led to a truly innovative solution. But if the AD axioms are to hold true in the Business Process design, the domains required substantial modification.

4.2 ADBP: Domains

In AD, the Customer Domain consists of the customer needs. The Functional domain specifies the functional requirements and constraints necessary to satisfy the customer needs. The physical domain is the domain in which design parameters are chosen to satisfy the functional requirement. The process domain specifies the process variables that can produce the design parameter.

The fundamental concept of Axiomatic Design for Business Process is that there are four domains in the design world for a business process in the regulated industry: Customer, Operational, Instructional, and Deliverable (see figure 1).



The Customer Domain remains the same and is described by the needs of the stakeholders for the process.

The Functional Domain is renamed the Operational Domain [OD] and is now described by the transformation of CN's into a high-level set of functional or Operational Requirements (OR) that describe "what the process does" to satisfy those CN's. The Operational Requirements become more specific consisting of the system based Standard Operational Requirements and operational constraints of the Business Process.

The Physical Domain is renamed to the Instructional Domain [ID] to better reflect the design activity that occurs at this stage of designing a Business Process in a regulated

industry. The Instructional Requirements do not really reflect the design parameters of the Business Process itself, rather they describe the translation of the high-level operational functions to the specific Instruction necessary to complete the standard operation. Therefore, this domain consists of the work instruction or business process steps in an instruction that supports the operational requirements in a procedure.

The Process Domain was also modified to be the Deliverable Domain. The Deliverable Domain describes the translation of instructional requirements into resulting deliverables or outputs needed to objectively show evidence of implementing the instructional requirements.

4.3 ADBP: Design Axioms

The common elements of all good designs remain the same as described by Nam Suh. Therefore, in ADBP, the same fundamental axioms, albeit with some revision to their definition, govern the analysis and decision making process in developing high quality product or system designs.

1) *Independence*: This axiom maintains and promotes the independence of various operational requirements, such that instructions may be modified to satisfy a particular operation without affecting the overall operational framework.

2) *Information*: This axiom states that the information content of alternative designs should be minimized, thus maximizing the success of the design.

The application of the axioms forces an organization and prioritization of requirements. Designs which do not satisfy the Independence Axiom are called coupled. Designs which satisfy the Independence Axiom, in the case of ADBP, are called decoupled. This is a major difference between AD and ADBP. The IRs are to be independent to its immediate operational requirement, however since a business operates cross-functionally, the individual operations and instructions will integrate. It is the author's experience that this integration is often overlooked, or not fully understood, within the typical design of a business process in the regulated industry.

In an acceptable design meeting the independence axiom, the IRs and ORs are related in such a way that a specific IR can be adjusted to satisfy its corresponding OR, but will impact the other ORs, as necessary, only in the case of integration points. Consequently, the order of adjusting the Instructional Requirements in a decoupled design is important.

Following this practice resulted in the necessary steps of the operation being defined as well as how the operations must work together. This resulted in pulling the otherwise independent instruction up into the overarching system of operations or operational framework. This approach may also be used for more complex systems where cross functionality is a constraint.

The application of the Information axiom focuses on achieving simplicity in the design and minimizing the information content necessary to select the best design solution. The design solution must have the smallest information content. The least

complicated or cumbersome the instruction the easier it is to realize achievement to meeting the operational requirements.

4.4 ADBP: Mapping and Hierarchy, and Zigzagging

The decomposition process to transform the operations into instructions between the domains is systematically analyzed using matrix methods. The design matrix begins with a systems perspective of the process and cross references and maps the instructional requirements from the top level, the operational framework, through each domain and hierarchy.

This alternating between pairs of domains to decompose the operations to instructions to deliverables is referred to as zigzagging as it is with AD. The hierarchies represent the design architecture and the decomposition process establishes the matrix mapping between ORs, IRs, and DRs.

The decomposition between the domains is represented by a design matrix, which shows the relationships between ORs and IRs.

This mapping can be summarized by: {OR} is the OR vector, {IR} is the IR vector, and [I] is the instructional design matrix, {OR} = [I] {IR}. An X or 0 in a cell indicates whether the column's IR affects the row's FR or not. The design matrix between the Operational Domain and the Instructional domain will be decoupled (Equation 3) as opposed to the truly uncouple solution one might seek in pure AD.

$$\begin{Bmatrix} OR1 \\ OR2 \end{Bmatrix} = \begin{bmatrix} X & O \\ O & X \end{bmatrix} \begin{Bmatrix} IR1 \\ IR2 \end{Bmatrix}$$

Equation 3ADBP Decoupled Design Equation

This is because each set of instructions designed in the instructional domain must work together as a system with integration points to each high-level operation in the Operational Domain. The key is to minimize these integration points to what is necessary and most simplistic for the same reasons using the AD methodology recommends gaining a truly uncoupled solution. This will still allow for independence between the instructions, but will support the instructions coming together into one overarching system operational concept.

$$\begin{Bmatrix} IR1 \\ IR2 \end{Bmatrix} = \begin{bmatrix} X & O \\ O & X \end{bmatrix} \begin{Bmatrix} DR1 \\ DR2 \end{Bmatrix}$$

Equation 4 ADBP Uncoupled Design Equation

The design matrix between the Instructional Domain and the Deliverables Domain should continue to strive for the uncoupled solution (Equation 4), but decoupled is also acceptable.

4.5 ADBP: Regulatory Lens and Zigzagging

The decomposition of the IR's developed in the Instructional Domain and DR's developed in the Deliverable Domain are complicated by the current regulatory environment and specific country interpretations of the standards and regulations that drive the needs for these types of business processes.

Specifically, according to AD methodology, constraints limit the choice of design parameters. Whereas in ADBP in the global regulated industry, constraints such as those found in process standards like ISO 14971, Medical Devices- Application of Risk Management to Medical Devices, or quality system regulations such as those found in ISO 13485:2003 might operate as a system constraint, one which is imposed by the system in which the design solution, or Business Process, must function.

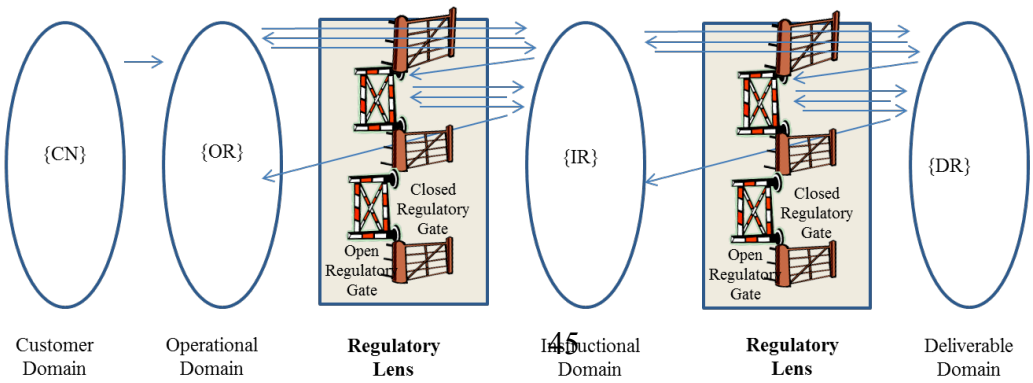
The implementation of these regulations and standards in the medical device industry, though, has become more risk based. So some regulatory requirements might constrain what functions have to be considered in a Business Process for the regulated industry, but they do not constrain how to do this. Therefore moving from the Operational Domain to the Instructional Domain, the Instructional Requirements that most simply satisfy the Operational Requirements are left up to interpretation, but are still dependent on the current regulatory environment of a given country. This "interpretation" is considered to be a "tolerance" or "ambiguity" to the regulation or standard. Even if a regulatory standard is harmonized across countries, the individual country's regulatory agency may have a different expectation for how to meet the requirements.

For example, in the case of a medical device with a radio component, constrained by ETSI EN 301 839, Electromagnetic Compatibility and Radio Spectrum Matters (ERM); Radio Equipment in the Frequency Range 402 MHz to 405 MHz for Ultra Low Power Active Medical Implants and Accessories, there may be a requirement to develop a protocol that provides the specific testing requirements for products related to their product performance characteristics. Even though a company designs and tests under the constraint of the standard, a specific country may wish for, or expects, verification testing to be done in their own country or by a designated lab, such as with some Asian countries. This is not a constraint of the standard itself, rather an expectation of that country based on the current regulatory environment.

The zigzagging process between the modified domains of ADBP, in the specific situation of designing a global Business Process in the Regulated Industry, therefore required a further need to modify and extend the AD methodology. Key to this significant modification is the introduction of the new term "Regulatory Tolerance" which is created and defined by this author as "a variable regulatory expectation, interpretation, or guidance, in an individual country or group of countries, based on the current regulatory environment of that country". In the regulated industry, it is necessary to review and accommodate this regulatory tolerance. Learning about or addressing this variable tolerance is often done at the later stages of the product development lifecycle, after the rejection of a regulatory submission or the unexpected inability to sell product into a specific country. Therefore, this significant and unique modification and extension of the AD methodology also includes what this author has designed as a Regulatory Lens.

This Regulatory Lens is a tool that is placed between the design domains of ADBP. When decomposing requirements, it must be done through this Regulatory Lens, forcing review of applicable regulatory tolerance at the front end of the lifecycle. When there is the case of possible tolerance, one would need to bounce against this lens, opening the regulatory gate for a specified requirement, as shown in the Regulatory Lens box of Figure 2, ADBP Domains with Regulatory Lens. When the gate is open, zigzagging occurs as normal between the domains. When the gate is closed by the designer, the zigzagging is halted between the domains and the zigzagging bounces against the closed gate until all country's tolerance for a given requirement is addressed. Once addressed, the gate re-opens and normal zigzagging resumes through the domains. So while a requirement may be for a protocol, regulatory tolerance identifies certain expectations for the execution of the protocol, and decomposing through the Regulatory Lens requires the determination of specific tolerance for each country of interest; such as execution of the protocol must be performed in-country, or by a particular lab.

These two significant and unique modifications and extensions to the AD methodology will simply and systematically address the interpretations of multiple countries for the same basic function resulting in the most robust global solution for the desired Business Process.



Chapter 5

COMPLIANCE FRAMEWORK – ADBP APPLIED

5.1 General

The business process subject to this research focuses on improving the product development lifecycle by optimizing the regulatory compliance workflow through this lifecycle. The solution must go beyond basic requirement management or tracing practices and must result in more control, the reduction of risk, and a cost return on investment. The intent of this section is to use ADBP to build an operational Compliance Framework that can be used and specified for biomedical device companies. There will be a highlighted section to indicate where the Regulatory Lens should be applied, but for the sake of the Framework, the requirements will be general. When using this Framework, the engineer would add the specifics for the give product technologies.

5.2 Internal Stakeholders

A business process within a medical device company ideally serves the needs of many cross functional stakeholders at all levels within an organization. Each stakeholder has a different need from the business process depending on what their role is in the organization. See Figure 3 as an example of stakeholders for a product development

process (Linehan, Pate-Cornell, & al, 2007). For example, some general points of view may be:

- Cross-Functional Upper management wants a simple and optimized business process. They want this process to reduce the required efforts associated with product development activities resulting in pushing more products through the pipeline while creating safer, compliant, and sellable devices.
- R&D Engineers want a process that defines required efforts in a way to reduce project risk related to requirements and compliance tracing and testing. They don't want this process to require them to have to create a lot of unnecessary or repetitive paperwork to be compliant.
- Regulatory Affairs ideally wants to be able to pull all of this objective evidence together to build a robust dossier for the regulatory agencies that includes clear evidence of compliance to applicable standards ensuring greater success of first time approval.
- Manufacturing Operations want the process to produce a product that they can manufacture.
- Quality Assurance wants to ensure that the development of a device meets all of the compliance requirements and that there is objective or supporting evidence to prove this
- Marketing and Sales wants the process to produce the right device that can be sold into the countries they want to sell.

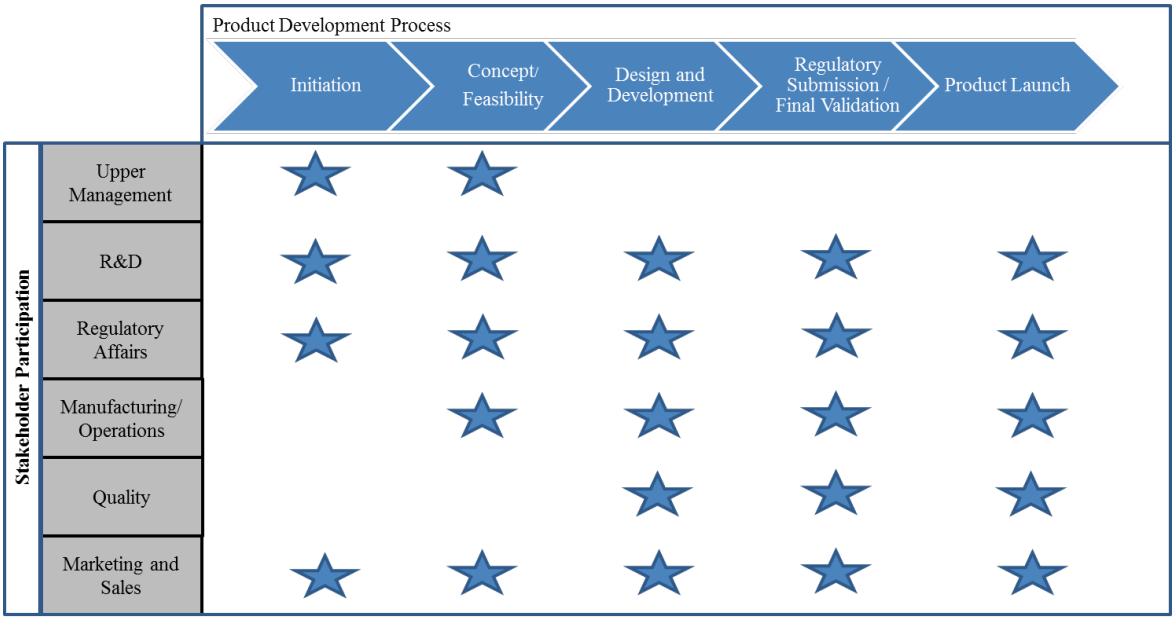


Figure 3 Examples of Stakeholders

5.3 External Interfaces

There are also external interfaces that impact these efforts within the product development process. These are interfaces, with impact, for which the organization has no real control. These external interfaces include:

- Regulatory agencies from around the world who identify what product development deliverables are required and in compliance to which standards.
- Reimbursement agencies

For the sake of this research, the outside stakeholders that impact the compliance chain of events are the regulatory agencies. Events and efforts associated with reimbursement requirements and impacts are outside of the scope of this research.

5.4 Customer Requirements

The Customer Domain describes the needs of the stakeholders. In this research, ADBP will be the applied design methodology used to develop a design solution to resolve and satisfy the following question:

"If we make an Implantable Biomedical Device that we want to sell globally, what kind of business processes do we need to develop to gain a competitive advantage in the future?"

Based on experience and input from engineering professionals (Easton D. , 2010), (Sobelman, July 2008), the following Customer Needs were determined:

CR1 A *simple* process that drives *efficiency*

CR2 A process that ensures global compliance for product technology

CR3 A Process that ensures global compliance for specific product

CR4 A process that supports entrance into the global market

CR5 A process that drives the "*right*" activities

5.5 Operational Requirements

The Operational Domain [OD] describes the transformation of CN's into a high-level set of functional or Operational Requirements (OR) that describe "what the process does" to satisfy those CN's. So the next phase of ADBP was to develop the Operational Requirements that will satisfy these customer needs. This must be done in a solution-neutral environment. In the case of this example, one must rely on both a technical understanding of the global regulatory environment and global standards, and the knowledge of typical Product Develop operations of a medical device organization.

Applying this type of knowledge, understanding, and experience, and implementing a systems approach to satisfying the global customer needs resulted in the following Operational Requirements:

FR1	Systemize the approach for compliance requirements
FR2	Standardize the approach where possible
FR3	Customize the information for specific project
FR4	Deliver and maintain compliant products for regulatory approvals for new product, new geographies, new indications, changes to regulatory environment

FR5 Define, Capture, and Sustain a system for Global Regulatory Compliance Information for Product Approvals

5.6 ADBP Requirements Development

5.6.1 Instructional Requirements

The Instructional Requirements describe the translation of the high-level operational functions to the specific Instruction necessary to complete the standard operation. Therefore, this domain consists of the work instruction or business process steps in an instruction that supports the operational requirements in a procedure.

Starting with the Operational Domain, it is required to move down the hierarchy, zigzagging between the domains to determine the requirements that can satisfy the requirements in the previous domain as well as determining where the Regulatory Lens must be applied between the domains. This process resulted in building the design architecture between the Domains. The blue highlighting represents where the user should incorporate use of the Regulatory Lens to address specific regulatory tolerance for countries of interest. When applying the framework in a specific situation, the user would proceed with the zigzagging through the regulatory gating process described above for their specific product technologies for their specific countries of interest. For example if a manufacturer was making a radio device, in the case of developing a labeling such as in IR3.8, there would be multiple deliverables taking into consideration the expectations of the country in which the device would be sold. Therefore, there

would be many DR 3.8.1, 3.8.2, 3.8.3, etc. that would map to IR 3.8. This effort resulted as in Table 1.

Table 1Translation of Operational Requirements to Instructional Requirements

Customer Domain		**Operational Domain**		**Instructional Domain**	
CR1	A *simple* process that drives *efficiency*	OR1	Systemize the approach for compliance requirements	IR1	Define steps to systemize compliance approach
		OR1.1	Define Product technology(ies) (eg., Implantables, nonimplantables, radio, surgical tools, accessories, etc.)	IR 1.1	Categorize product technology types
				IR1.1.1	Define indications for use for products
		OR1.2	Define typical countries of sale for products (eg. US, EEA, Japan,	IR1.2	Categorize countries for each product technology

		Canada, Australia, New Zealand, etc.)		
	OR1.3	Define Compliance areas (product and process such as biocompatibility, Sterilization, Packaging, Labeling, Risk Management, Usability, Environmental)	IR1.3	Categorize compliance areas for each product technology
	OR1.4	Define general types of required approvals for product technology (eg. Medical, Radio)	IR1.4	Capture general approval types
	OR1.5	Define at high level the regulatory information necessary to sell these product	IR1.5	Capture directives, standards, laws for each product technology for each

	technologies - directives, standards, national legislation, laws		country of interest
OR1.6	Generate Compliance Matrix	IR1.6	Capture data for Matrix
OR1.7	Define applicability of regulatory information	IR1.7	Capture applicability and justification for non-applicability for each product technology for each country of interest
OR1.8	Define applicability, by clause, of regulatory information	IR1.8	Capture applicability and justification for non-applicability of each clause detail of the regulatory information for each product technology for each country of

			interest
OR1.9	Define regulatory tolerance by countries of interest	IR1.9 Regulatory Lens	Categorize areas of difference between countries (submission documentation, testing, expectation, etc.)
		IR1.9.1	Categorize countries by like compliance requirements
		IR1.9.2	Capture country specific regulatory tolerance for applicable regulatory information
OR1.10	Define requirements associated with applicable regulatory information (eg design and test	IR1.10	Capture requirements and constraints from standards

			requirements)		
		OR1.11	Associate compliance requirements with product requirements	IR1.11	Capture associated product requirement
		OR1.12	Associate product requirements with related testing requirements	IR 1.12	Capture associated generic verification test methods
CR2	A process that ensures global compliance for product technology	OR2	Standardize compliance with tools that inherently trace to compliance requirements	IR2	Define steps or tools to standardize compliance
		OR2.1	Define process compliance requirements that can be standardized	IR2.1	Capture standard process compliance requirements (e.g. usability, biocompatibility,

				sterility assurance, risk management, etc.)
	OR2.2	Define product performance test types for product technologies	IR2.2	Categorize test types (electrical, mechanical, system)
	OR2.3	Define product performance compliance requirements that can be standardized	IR2.3	Capture standard product performance requirements
	IR2.4	Define compliance implementation measures at product and system levels for countries of interest: in-country testing, method of measurement/ test methods, specified	IR2.4 Regulatory Lens	Capture specific country expectations in protocols or WI's

		test house, etc.		
	IR2.5	Define which test methods are standard and repeatable	IR2.5	Capture product performance acceptance criteria by test type
			IR2.5.1	Capture standardized product performance test methods for independent test types for product technologies
			IR2.5.2 Regulatory Lens	Capture system level interaction between the parts are not covered in independent product protocols.
	IR2.6	Ensure standardized compliance requirements	IR2.6	Capture compliance requirements inherently

CR3	A Process that ensures global compliance for specific NPD project	OR3	Customize the information for specific project	IR3	Define steps or instructions to customize System and standard compliance information for NPD
		OR3.1	Define product technology for NPD project	IR3.1	Capture significant differences
		OR3.2	Define relevant standards for NPD project from standards list for product technology, countries of sale, and indication	IR3.2	Capture list of relevant standards
IR3.		OR3.3	Compare and reconcile project		update, revise, or develop new

3		requirements to the systematized and standardized compliance information for product technologies.		systematized or standardized outputs
	OR3.4	Define project specific requirements	IR3.4	Capture system level Compliance requirements
			IR3.4.1	Capture product level compliance requirements
	OR3.5	Ensure project requirements are mapped to compliance requirements	IR3.5	Capture mapping between compliance requirements and WI, Generic Protocols unique identifiers
			IR3.5.1	Capture mapping between requirements and specific project documentation unique

				identifiers
	OR3.6	Customize applicable compliance requirements	IR3.6	create a compliance plan
	OR3.7	Customize process based compliance requirements as necessary for specific project	IR3.7	Implement WI's associated with meeting regulatory compliance requirements (e.g. usability, risk management, etc.)
	OR3.8	Customize labeling for countries of interest, for indication, for product technology.	IR3.8 Regulatory Lens	Ensure presence of appropriate labeling for all countries of interest for project
	OR3.9	Customize project specific product and system level	IR3.9	Document in product specifications

		testing		
	OR3.10	create project specific protocols as necessary	IR3.10	Develop protocol that provides the specific testing requirements for products related to their product performance characteristics, as necessary.
			IR3.10.1	Develop protocol that provides the specific methods for product tests related to particular compliance requirements (e.g. electrical and mechanical performance requirements.) as necessary
			IR3.10.	Develop protocol that provides specific

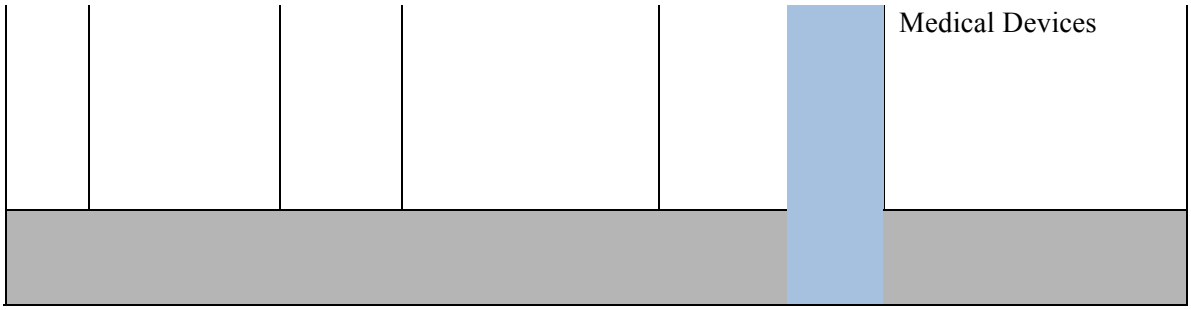
				2	system level tests related to system level interaction between the parts are not covered in individual product protocols, as necessary
				IR3.10. 3	Implement protocols associated with meeting regulatory compliance requirements (e.g. usability, risk management, etc.)
CR4	A process that supports entrance into the global market	OR4	Deliver and maintain compliant products for regulatory approvals for new product, new geographies, new indications,	IR4	WI to provide input to summary technical Documentation for demonstrating Conformity to the Essential Principles of safety and performance of

			changes to regulatory environment		Medical Devices
		OR4.1	Ensure adequacy and availability of appropriate deliverables for approval types, for all planned countries of sale for the project.	IR4.1	Capture project specific compliance requirements in final trace
				IR4.1.1	Create applicable compliance checklists necessary for approvals (e.g. Essential Requirements Checklist)
		OR4.2	Certify development of project to regulations	IR4.2 Regulatory Lens	Develop certificates of conformance to applicable regulations and standards as per

						country expectations
		OR4.3	assure product compliance can be sustained through design changes, labeling changes, safety changes, regulatory changes, etc.	IR4.3	Regulatory Lens	Ensure adequacy and availability of appropriate deliverables for approval types, for all planned countries of sale for recertification's, changes to regulations, new countries of interest, new indications.
		OR4.4	compare project based requirements to the systematized and standardized tools that document requirements for product	IR4.4	Regulatory Lens	Reconcile project based products/process requirements against Generic systematized and standardized regulatory information

			technologies.			
CR5	A process that drives the "*right*" activities	OR5	Define framework to Sustain best practices for managing Global Regulatory Compliance	IR5	Regulatory Lens	Capture defined processes and link together
		OR5.1	SOP to systematize compliance information by product technologies	IR5.1		Work Instruction to explain how to define, capture, and maintain global compliance information
		OR5.2	SOP to standardized compliance efforts	IR5.2		Tools that Inherently trace compliance throughout Product Development and business operations

		OR5.3	SOP for New Product Development	IR5.3		link to WI/Integration of compliance efforts into existing design controls process
		OR5.4	SOP for New indications for use or New geographies	IR5.4		link to WI to provide input to summary technical Documentation for demonstrating Conformity to the Essential Principles of safety and performance of Medical Devices
		OR5.5	SOP for New or Revised Standards	IR5.5		



5.6.2 Deliverable Requirements

The Deliverable Domain describes the translation of instructional requirements into resulting deliverables or outputs needed to objectively show evidence of implementing the instructional requirements (Table 2).

Table 2 Translation IRs to DRs

	Instructional Domain		**Deliverable Domain**
IR1	Define steps to systemize compliance approach	DR1	Document output in controlled database
IR 1.1	Categorize product technology types	DR1.1	Create list of product technologies in

			database
IR1.1.1	Define indications for use for products	DR1.1.1	create list of indications for use
IR1.2	Categorize countries for each product technology	DR1.2	Create list of countries of interest in database
IR1.3	Categorize compliance areas for each product technology	DR1.3	Create list of compliance areas in database
IR1.4	Capture general approval types	DR1.4	Create a list of approval types in database
IR1.5	Capture directives, standards, laws for each product technology for each	DR1.5	Create lists of Regulatory Information in

	country of interest		Database
		DR1.5.1	Create list of Directives in Database
		DR1.5.2	Create list of standards in database
		DR1.5.3	Create list of laws or national legislation in Database
		DR1.5.4	Create link between approval type and regulatory information
IR1.6	Capture data for Matrix	DR1.6	Create fields in database

			DR1.6.1	create field for product technology
			DR1.6.2	create field for regulatory information
			DR1.6.3	create field for country of interest
			DR1.6.4	create field for approval type
			DR1.6.5	create field for compliance area
			DR1.6.6	create field for country of sale
			DR1.6.7	create applicability selection
			DR1.6.8	create field for

			non-applicability justification
		DR1.6.9	create field for country category
		DR1.6.10	create field for regulatory tolerance
		DR1.6.11	create field for clause
		DR1.6.12	create field for requirement
		DR1.6.13	create field for product requirement
		DR1.6.14	create field for test method
IR1.7	Capture applicability and justification for	DR1.7	Document what regulatory information,

	non-applicability for each product technology for each country of interest		from which compliance category, for each product technology, for each country of interest is applicable. Document justification if not applicable.
IR1.8	Capture applicability and justification for non-applicability of each clause detail of the regulatory information for each product technology for each country of interest	DR1.8	Document what clause for each standard is applicable. Document justification if not applicable.

IR1.9	Regulatory Lens	Categorize areas of difference between countries (submission documentation, testing, expectation, etc.)	DR1.9	create list of Areas of Difference
IR1.9.1		Categorize countries by like compliance requirements	DR1.9.1	create list for country category (e.g. tier1, tier 2, etc.)
IR1.9.2		Capture country specific regulatory tolerance for applicable regulatory information	DR1.9.2	Document country specific regulatory tolerance.
IR1.10		Capture requirements and constraints from	DR 1.10	Document requirements and constraints from applicable

	standards		clauses
IR1.11	Capture associated product requirement	DR1.11	Document associated product requirements
IR 1.12	Capture associated generic verification test methods	DR1.12	Document associated test method and/or test standard
IR2	Define steps or tools to standardize compliance	DR2	Document output
IR2.1	Capture standard process compliance requirements (e.g. usability, biocompatibility, sterility assurance,	DR2.1	Document in controlled work instructions

		risk management, etc.)		
IR2.2		Categorize test types (electrical, mechanical, system)	DR2.2	Document test types
IR2.3		Capture standard product performance requirements	DR2.3	Document in generic protocols
IR2.4	Regulatory Lens	Capture specific country expectations in protocols or WI's	DR2.4	Document in WIs or protocols
IR2.5		Capture product performance acceptance criteria by test type	DR2.5	Document acceptance criteria in controlled generic protocol

IR2.5.1	Capture standardized product performance test methods for independent test types for product technologies	DR2.5.1	Document test methods for independent test types in controlled generic protocols
IR2.5.2	Capture system level interaction between the parts are not covered in independent product protocols.	DR2.5.2	Document test methods for system test type in controlled generic protocols
IR2.6	Capture compliance requirements inherently	DR2.6	document reference to specific standards requirement in protocol

		DR2.6.1	document reference to specific Standards requirements in WIs.
IR3	Define steps or instructions to customize System and standard compliance information for NPD	DR3	Document in project specific deliverables
IR3.1	Capture significant differences	DR3.1	Document in Customer Specifications
IR3.2	Capture list of relevant standards	DR3.2	document in specification documents

IR3.3	update, revise, or develop new systematized or standardized outputs	DR3.3	document in controlled documents
IR3.4	Capture system level Compliance requirements	DR3.4	document in product specifications
IR3.4.1	Capture product level compliance requirements	DR3.4.1	document in product specifications
IR3.5	Capture mapping between compliance requirements and WI, Generic Protocols unique identifiers	DR3.5	Document in field in compliance trace matrix
IR3.5.1	Capture mapping between	DR3.5.1	Document in field in

	requirements and specific project documentation unique identifiers		compliance trace matrix
IR3.6	create a compliance plan	DR3.6	Generate a planning column in compliance trace that maps the expected evidence of conformity (process and product) to applicable compliance requirements
IR3.7	Implement WI's associated with meeting regulatory compliance requirements (e.g.	DR3.7	review, approve, and control deliverables of Wis.

		usability, risk management, etc.)			
IR3.8	Regulatory Lens	Ensure presence of appropriate labeling for all countries of interest for project	DR3.8	Regulatory Lens	Review and approved the project specific labeling
IR3.9		Document in product specifications	DR3.9		review and approve the project specific product requirement specification documents to

				documents.
IR3.10		Develop protocol that provides the specific testing requirements for products related to their product performance characteristics, as necessary.	DR3.10	Generate column in compliance trace identifying by clause the testing requirements associated with the standards
IR3.10.1			DR3.10.1	
		Develop protocol that provides the specific methods for product tests		Generate column in compliance trace identifying product test

		performance requirements.) as necessary			associated compliance requirement.
IR3.10.2		Develop protocol that provides specific system level tests related to system level interaction between the parts are not covered in individual product protocols, as necessary	DR3.10.2		independently review and approve the verification and validation protocols to ensure that the testing performed per these documents is consistent with compliance requirements from appropriate standards and regulations.

IR3.10.3	Implement protocols associated with meeting regulatory compliance requirements (e.g. usability, risk management, etc.)	DR3.10.3	Document results in report
		DR3.10.3.1	independently review and approve the verification and validation reports to ensure that the testing performed per these documents is consistent with compliance requirements from appropriate standards and

			regulations.
IR4	WI to provide input to summary technical Documentation for demonstrating Conformity to the Essential Principles of safety and performance of Medical Devices	DR4	final compliance trace with summary of test results
IR4.1	Capture project specific compliance requirements in final trace	DR4.1	review the technical information as well as the labeling related information for

			submissions to all countries in the initial regulatory submission plan.
IR4.1.1	Create applicable compliance checklists necessary for approvals (e.g. Essential Requirements Checklist)	DR4.1.1	Create final comprehensive compliance trace for project/products with row of compliance categories (product and process such as biocompatibility, Sterilization, Packaging, Labeling, Risk Management, Usability, Environmental)

				and column of applicable directives, standards, and clauses, summary of testing methods, summary of test results, mapping of evidence of conformity to requirements.
IR4.2	Regulatory Lens	Develop certificates of conformance to applicable regulations and standards as per country expectations	DR4.2	Sign and deliver CofC to Regulatory Affairs to include in product submissions
			DR4.2.2	For 510(k) submissions to

				FDA, fill out the form 36543 for each standard that the project claims conformity to.
IR4.3		Ensure adequacy and availability of appropriate deliverables for approval types, for all planned countries of sale for recertification's, changes to regulations, new countries of interest, new indications.	DR4.3	Regulatory Lens Sustaining compliance WI

IR4.4	Reconcile project based products/process requirements against Generic systematized and standardized regulatory information	DR4.4	update, revise, or develop new systematized, standardized, or customized outputs
IR5	Capture defined processes and link together	DR5	Document integration in system framework
IR5.1		DR5.1	

Document integration in system framework

		information		
IR5.2		Tools that Inherently trace compliance throughout Product Development and business operations	DR5.2	Document integration in system framework
IR5.3		link to WI/Integration of compliance efforts into existing design controls process	DR5.3	Document integration in system framework
IR5.4			DR5.4	
		link to WI to provide input to summary technical Documentation for		Document integration in system framework

		performance of Medical Devices		
IR5.5		Link to WI to provide input to summary technical Documentation for demonstrating Conformity to the Essential Principles of safety and performance of Medical Devices	DR5.5	Document integration in system framework

5.6.3 Design Architecture

Requirements development resulted in the following design architecture depicted in Table 3 and more traditionally, as in Figure 4.

Table 3 Design Architecture

Customer Domain		Operational Domain		Instructional Domain		Deliverable Domain	
CR1	A *simple* process that drives *efficiency*	OR1	Systemize the approach for compliance requirements	IR1	Define steps to systemize compliance approach	DR1	Document output in controlled database
		OR1.1	Define Product technology(ies) (eg., Implantables, nonimplantables, radio, surgical tools, accessories, etc.)	IR 1.1	Categorize product technology types	DR1.1	Create list of product technologies in database
				IR1.1.1	Define indications for use for products	DR1.1.1	create list of indications for use
		OR1.2	Define typical countries of sale for products (eg.	IR1.2	Categorize countries for each product	DR1.2	Create list of countries of interest in

		US, EEA, Japan, Canada, Australia, New Zealand, etc.)		technology		database
	OR1.3	Define Compliance areas (product and process such as biocompatibility, Sterilization, Packaging, Labeling, Risk Management, Usability, Environmental)	IR1.3	Categorize compliance areas for each product technology	DR1.3	Create list of compliance areas in database
	OR1.4	Define general types of required approvals for product technology (eg. Medical, Radio)	IR1.4	Capture general approval types	DR1.4	Create a list of approval types in database

	OR1.5	Define at high level the regulatory information necessary to sell these product technologies - directives, standards, national legislation, laws	IR1.5	Capture directives, standards, laws for each product technology for each country of interest	DR1.5	Create lists of Regulatory Information in Database
					DR1.5.1	Create list of Directives in Database
					DR1.5.2	Create list of standards in database
					DR1.5.3	Create list of laws or national legislation in Database

				DR1.5.4	Create link between approval type and regulatory information
	OR1.6 Generate Compliance Matrix	IR1.6	Capture data for Matrix	DR1.6	Create fields in database
				DR1.6.1	create field for product technology
				DR1.6.2	create field for regulatory information
				DR1.6.3	create field for country of interest
				DR1.6.4	create field for approval type
				DR1.6.5	create field for compliance area
				DR1.6.6	create field for

					country of sale
				DR1.6.7	create applicability selection
				DR1.6.8	create field for non-applicability justification
				DR1.6.9	create field for country category
				DR1.6.10	create field for regulatory tolerance
				DR1.6.11	create field for clause
				DR1.6.12	create field for requirement
				DR1.6.13	create field for product requirement
				DR1.6.14	create field for

					test method
OR1.7	Define applicability of regulatory information	IR1.7	Capture applicability and justification for non-applicability for each product technology for each country of interest	DR1.7	Document what regulatory information, from which compliance category, for each product technology, for each country of interest is applicable. Document justification if not applicable.
OR1.8	Define applicability, by clause, of regulatory information	IR1.8	Capture applicability and justification for non-applicability of each clause detail of the regulatory information	DR1.8	Document what clause for each standard is applicable. Document justification if not applicable.

				for each product technology for each country of interest		
OR1.9	Define regulatory tolerance by countries of interest	IR1.9	Regulatory Lens	Categorize areas of difference between countries (submission documentation, testing, expectation, etc.)	DR1.9	create list of Areas of Difference
		IR1.9.1		Categorize countries by like compliance requirements	DR1.9.1	create list for country category (e.g. tier1, tier 2, etc.)
		IR1.9.2		Capture country specific regulatory tolerance for	DR1.9.2	Document country specific regulatory tolerance.

				applicable regulatory information		
	OR1.10	Define requirements associated with applicable regulatory information (eg design and test requirements)	IR1.10	Capture requirements and constraints from standards	DR 1.10	Document requirements and constraints from applicable clauses
	OR1.11	Associate compliance requirements with product requirements	IR1.11	Capture associated product requirement	DR1.11	Document associated product requirements
	OR1.12	Associate product requirements with related testing requirements	IR 1.12	Capture associated generic verification test methods	DR1.12	Document associated test method and/or test standard

CR 2	A process that ensures global compliance for product technology	OR2	Standardize compliance with tools that inherently trace to compliance requirements	IR2	Define steps or tools to standardize compliance	DR2	Document output
		OR2.1	Define process compliance requirements that can be standardized	IR2.1	Capture standard process compliance requirements (e.g. usability, biocompatibility, sterility assurance, risk management, etc.)	DR2.1	Document in controlled work instructions
		OR2.2	Define product performance test types for product technologies	IR2.2	Categorize test types (electrical, mechanical, system)	DR2.2	Document test types

	OR2.3	Define product performance compliance requirements that can be standardized	IR2.3		Capture standard product performance requirements	DR2.3	Document in generic protocols
	IR2.4	Define compliance implementation measures at product and system levels for countries of interest: in-country testing, method of measurement/ test methods, specified test house, etc.	IR2.4	Regulatory Lens	Capture specific country expectations in protocols or WI's	DR2.4	Document in WIs or protocols
	IR2.5	Define which test methods are standard and repeatable	IR2.5		Capture product performance acceptance criteria by test	DR2.5	Document acceptance criteria in controlled generic

				type		protocol
			IR2.5.1	Capture standardized product performance test methods for independent test types for product technologies	DR2.5.1	Document test methods for independent test types in controlled generic protocols
			IR2.5.2	Capture system level interaction between the parts are not covered in independent product protocols.	DR2.5.2	Document test methods for system test type in controlled generic protocols
		IR2.6	Ensure standardized compliance requirements	IR2.6	Capture compliance requirements inherently	DR2.6	document reference to specific standards requirement in

							protocol
					DR2.6.1		document reference to specific Standards requirements in WIs.
CR3	A Process that ensures global compliance for specific NPD project	OR3	Customize the information for specific project	IR3	Define steps or instructions to customize System and standard compliance information for NPD	DR3	Document in project specific deliverables
		OR3.1	Define product technology for NPD project	IR3.1	Capture significant differences	DR3.1	Document in Customer Specifications
		OR3.2	Define relevant standards for NPD project from standards	IR3.2	Capture list of relevant standards	DR3.2	document in specification documents

		list for product technology, countries of sale, and indication				
	OR3.3	Compare and reconcile project requirements to the systematized and standardized compliance information for product technologies.	IR3.3	update, revise, or develop new systematized or standardized outputs	DR3.3	document in controlled documents
	OR3.4	Define project specific requirements	IR3.4	Capture system level Compliance requirements	DR3.4	document in product specifications
			IR3.4.1	Capture product level compliance requirements	DR3.4.1	document in product specifications

	OR3.5	Ensure project requirements are mapped to compliance requirements	IR3.5	Capture mapping between compliance requirements and WI, Generic Protocols unique identifiers	DR3.5	Document in field in compliance trace matrix
			IR3.5.1	Capture mapping between requirements and specific project documentation unique identifiers	DR3.5.1	Document in field in compliance trace matrix
	OR3.6	Customize applicable compliance requirements	IR3.6	create a compliance plan	DR3.6	Generate a planning column in compliance trace that maps the expected evidence of

									conformity (process and product) to applicable compliance requirements
	OR3.7	Customize process based compliance requirements as necessary for specific project	IR3.7		Implement WI's associated with meeting regulatory compliance requirements (e.g. usability, risk management, etc.)	DR3.7			review, approve, and control deliverables of Wis.
	OR3.8	Customize labeling for countries of interest, for indication, for product technology.	IR3.8	Regulatory Lens	Ensure presence of appropriate labeling for all countries of interest for project	DR3.8	Regulatory Lens		Review and approved the project specific labeling

							review and approve the project specific product requirement specification documents to ensure that compliance requirements from appropriate standards and regulations are included in these documents.
	OR3.9	Customize project specific product and system level testing	IR3.9	Document in product specifications	DR3.9		
	OR3.10	create project specific protocols as necessary	IR3.10	Develop protocol that provides the specific testing requirements	DR3.10		

				characteristics, as necessary.			the standards
			IR3.10.1	Develop protocol that provides the specific methods for product tests related to particular compliance requirements (e.g. electrical and mechanical performance requirements.) as necessary	DR3.10.1		Generate column in compliance trace identifying product test methods, acceptance criteria, # of samples, etc. and mapping to the associated compliance requirement.
			IR3.10.2		DR3.10.2		independently review and approve the verification
				Develop protocol that provides specific system level tests			and validation protocols to ensure that the

					interaction between the parts are not covered in individual product protocols, as necessary		testing performed per these documents is consistent with compliance requirements from appropriate standards and regulations.
				IR3.10.3	Implement protocols associated with meeting regulatory compliance requirements (e.g. usability, risk management, etc.)	DR3.10.3	Document results in report

						DR3.10.3.1	independently review and approve the verification and validation reports to ensure that the testing performed per these documents is consistent with compliance requirements from appropriate standards and regulations.
CR4	A process that supports entrance into the global	OR4	Deliver and maintain compliant products for regulatory approvals for new product,	IR4	WI to provide input to summary technical Documentation for demonstrating	DR4	final compliance trace with summary of test results

	market		new geographies, new indications, changes to regulatory environment		Conformity to the Essential Principles of safety and performance of Medical Devices		
		OR4.1	Ensure adequacy and availability of appropriate deliverables for approval types, for all planned countries of sale for the project.	IR4.1	Capture project specific compliance requirements in final trace	DR4.1	review the technical information as well as the labeling related information for submissions to all countries in the initial regulatory submission plan.

				IR4.1.1	Create applicable compliance checklists necessary for approvals (e.g. Essential Requirements Checklist)	DR4.1.1	Create final comprehensive compliance trace for project/products with row of compliance categories (product and process such as biocompatibility, Sterilization, Packaging, Labeling, Risk Management, Usability, Environmental) and column of applicable directives, standards, and clauses, summary of testing methods, summary of

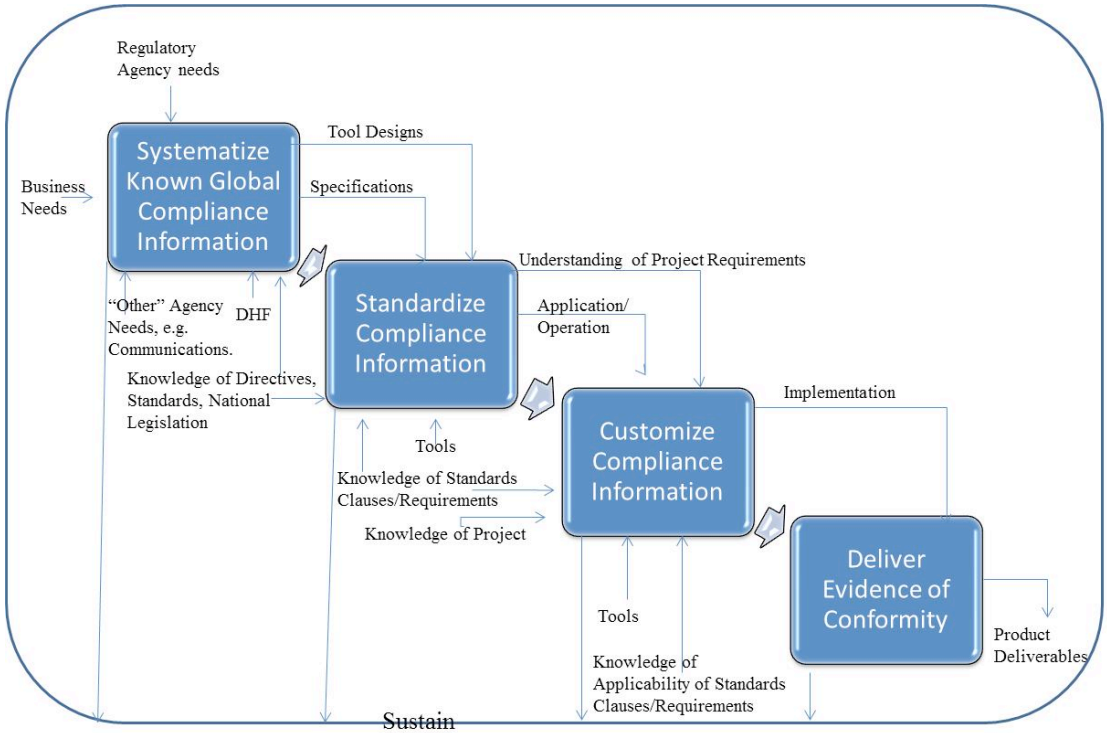
								test results, mapping of evidence of conformity to requirements.
		OR4.2	Certify development of project to regulations	IR4.2	Regulatory Lens	Develop certificates of conformance to applicable regulations and standards as per country expectations	DR4.2	Sign and deliver CofC to Regulatory Affairs to include in product submissions
							DR4.2.2	For 510(k) submissions to FDA, fill out the form 36543 for each standard that the project claims conformity to.

		OR4.3	assure product compliance can be sustained through design changes, labeling changes, safety changes, regulatory changes, etc.	IR4.3	Ensure adequacy and availability of appropriate deliverables for approval types, for all planned countries of sale for recertification's, changes to regulations, new countries of interest, new indications.	DR4.3	Regulatory Lens	Sustaining compliance WI
		OR4.4	compare project based requirements to the systematized and standardized tools that document requirements for product	IR4.4	Reconcile project based products/process requirements against Generic systematized and standardized regulatory information	DR4.4		update, revise, or develop new systematized, standardized, or customized outputs

			technologies.				
CR 5	A process that drives the "*right*" activities	OR5	Define framework to Sustain best practices for managing Global Regulatory Compliance	IR5	Capture defined processes and link together	DR5	Document integration in system framework
		OR5.1	SOP to systematize compliance information by product technologies	IR5.1	Work Instruction to explain how to define, capture, and maintain global compliance information	DR5.1	Document integration in system framework
		OR5.2	SOP to standardized compliance	IR5.2	Tools that Inherently trace	DR5.2	Document integration in system

	efforts			compliance throughout Product Development and business operations		framework
OR5.3	SOP for New Product Development	IR5.3		link to WI/Integration of compliance efforts into existing design controls process	DR5.3	Document integration in system framework
OR5.4	SOP for New indications for use or New geographies	IR5.4			DR5.4	
				link to WI to provide input to summary technical		Document integration in system framework

					Devices		
		OR5.5	SOP for New or Revised Standards	IR5.5	Link to WI to provide input to summary technical Documentation for demonstrating Conformity to the Essential Principles of safety and performance of Medical Devices	DR5.5	Document integration in system framework



5.6.4 ADBP Requirements Analysis

From the ADBP architecture the product operation and instruction matrix can be created. The goal is to satisfy the two axioms of information and independence. Due to the nature of a process being cross functional, a completely uncoupled solution is not possible or desirable, as mentioned before. As represented in the design architecture, ultimately, the system of operations must all come together to build a sustainable system under one primary and overarching sustainable operational concept.

Mapping the Operational Requirements against the Instructional Requirements and the Instructional Requirements against the Deliverable Requirements creates the matrices below. This satisfies the independence axiom by creating decoupled matrices as seen by the red triangles.

	IR1	IR2	IR3	IR4	IR5
OR1	X				
OR2	X	X			
OR3	X	X	X		
OR4			X	X	
OR5	X	X	X	X	X

Figure 5 ADBP OR-IR Design Matrix

	DR1	DR2	DR3	DR4	DR5
IR1	X				
IR2		X			
IR3	X	X	X		
IR4		X	X	X	
IR5					X

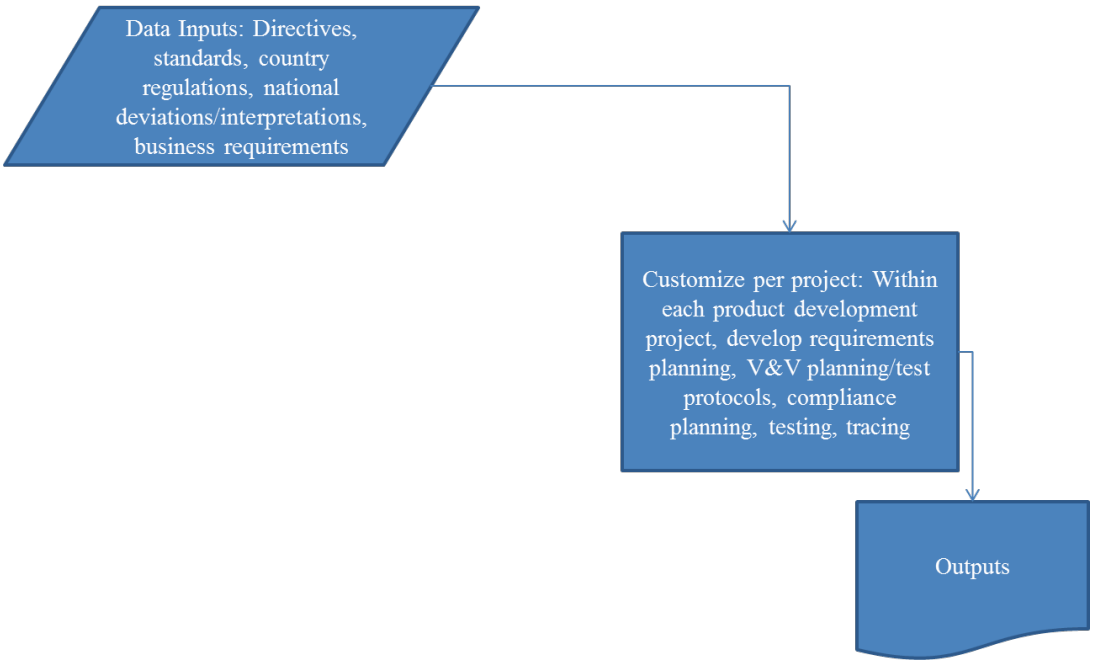
Figure 6 ADBP IR-DR Design Matrix

Chapter 6

COMPLIANCE FRAMEWORK

6.1 Operational Concept

Applying ADBP led to the creation of the operational Compliance Framework for developing and implementing a business process around compliance requirements. Typically compliance is addressed for each individual project is the project by project approach shown in Figure 7.



The design solution using ADBP has developed a different, better, approach. This operational framework is shown in Figure 8 and reflects the decoupled solution resulting from the requirements breakdown. The red box encompasses the part of work that is done comprehensively one time only. This information is reviewed for each project, but only the work pertaining to the delta between a new development project and what has been developed as part of the systematize and standardize part of the concept, in the form of specifications, protocols, instructions, etc. will be leveraged for the individual project. This will thereby give back time to the project teams who would have been addressing these compliance efforts on the project by project approach.

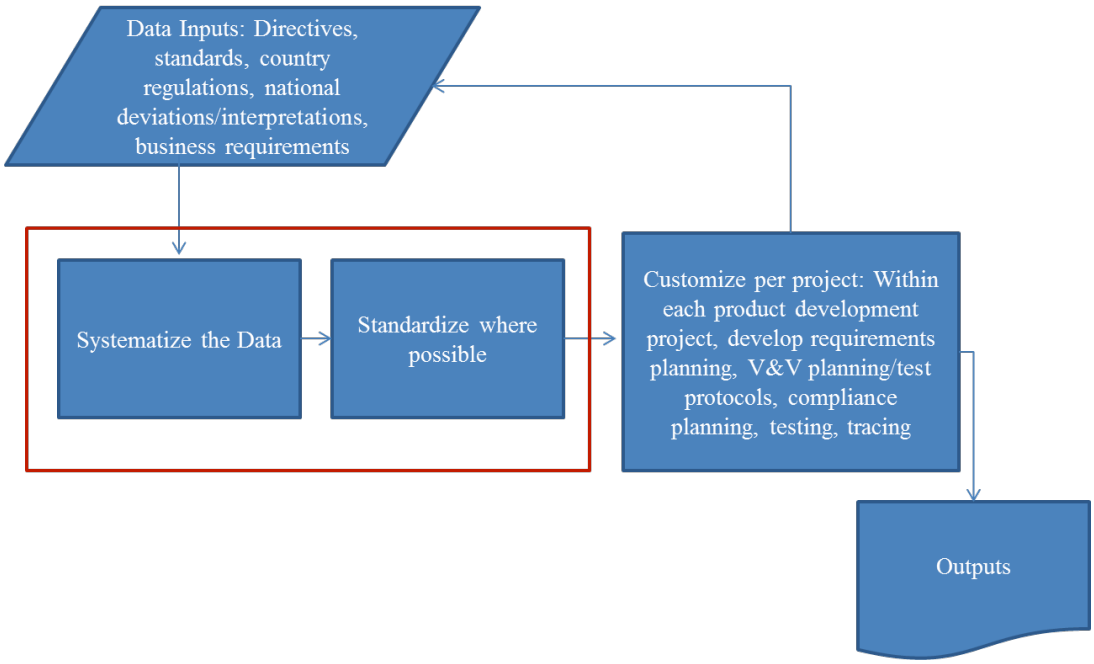


Figure 8 ADBP Compliance Framework

Chapter 7

VALIDATION OF COMPLIANCE FRAMEWORK

7.1 General

It was hypothesized, in this part of the research, that applying the "Compliance Framework", which was derived based on new extensions to the Axiomatic Design process, in the medical device industry will afford companies more time for innovation, reduce compliance risk, and ultimately push product through the pipeline faster and smarter, with limited re-do or rework iterations within the process. The method of validation used was to model the chain of the regulatory compliance pathway through a current product development process, defining time, manpower, and typical range of iterations through these steps. Then the intent was to apply the Compliance Framework to obtain a proposed process that shows the decrease in time and iterations for these steps thereby proving the Compliance Framework as an optimal approach to the regulatory compliance efforts within a product development process in the regulated industry.

7.2 Current Product Development Model

Stanford University's Program in Biodesign conducted a study on Medical Device Development Models which was completed in September 2007 (Linehan, Pate-Cornell,

& al, 2007). The purpose of this study was, in part, to gain a thorough understanding of the medical device innovation, or product development, process and development pathways. It intended to present a comprehensive description of the medical device development process in order to help inform the public about the specific nature of medical devices and their development processes in particular. The focus in this study was the regulatory environment in the US and the cross-functional resources involved with this process (Linehan, Pate-Cornell, & al, 2007).

Through a sound methodology described in detail in *Study of Medical Device Development Models*, Figure 9 depicts a high level, cross-functional development model that applies to most all technologies and organization size. This is possible because the Quality System regulations mandate elements of a design process including: definition of design input, design output, specification development, testing, risk analysis, process qualification, etc. It is stage-gated and comprises five phases from Initiation /Opportunity and Risk Analysis to Post-Launch and Post-Launch Surveillance (Linehan, Pate-Cornell, & al, 2007).

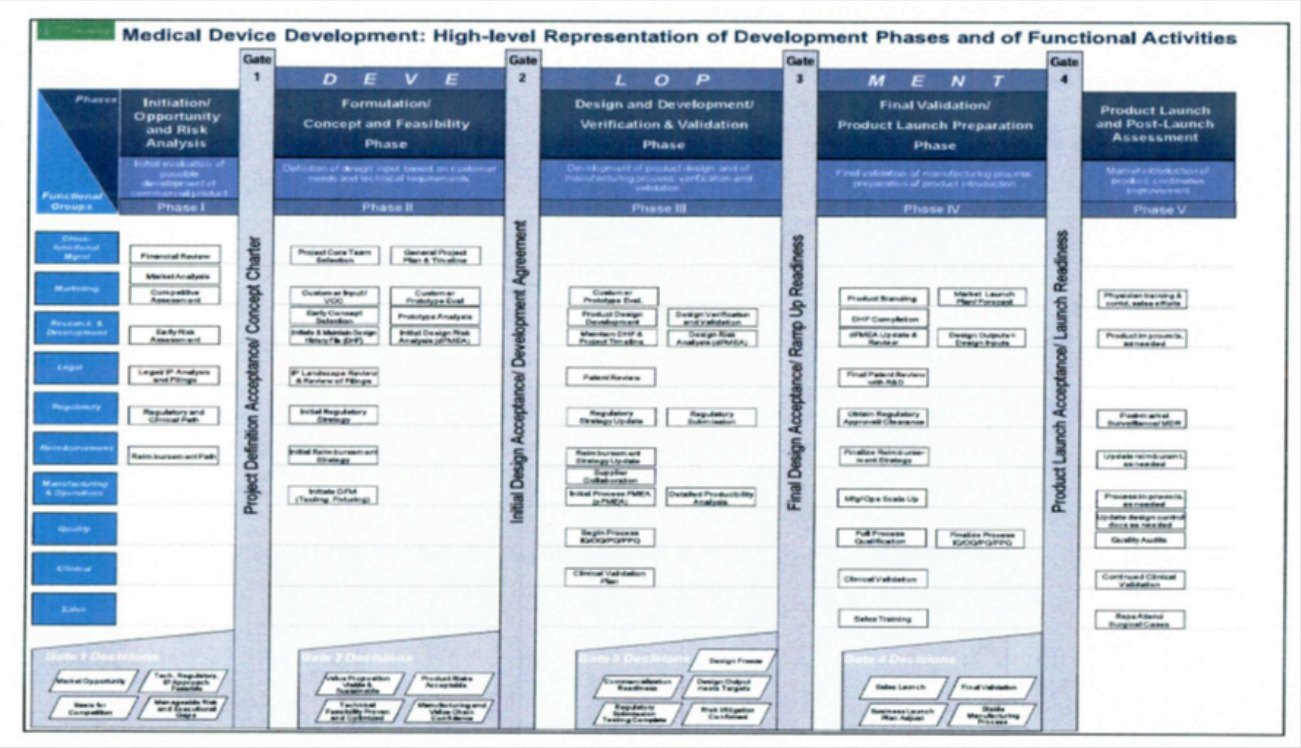


Figure 9 Stanford BioDesign Medical Device Development Model

As stated in the Stanford BioDesign Study on Medical Device Development Models, "The study shows that significant aspects of the development process are governed by, or at least subject to, regulatory requirements. These requirements significantly impact the way in which medical devices are developed and brought to market – not only in terms of time to approval, but also in terms of the way in which development is conducted." (Linehan, Pate-Cornell, & al, 2007)

The focus of this research is on improving a subset of the comprehensive development model, the regulatory pathway through the Product Development lifecycle. From the Standford BioDesign Model, Figure 10 depicts this pathway and the specific development activities and decisions affected by regulatory requirements and is the basis of the "current" model. At each stage in the development process for a medical device,

there are steps that must occur and decision points that determine whether the development teams can move on to the next stage. These steps represent the work flow through the product development process as it relates to regulatory activities. Table 7 details specific regulatory activities that would occur at each stage of the product development process and some decisions points that are influenced by the regulatory workflow.

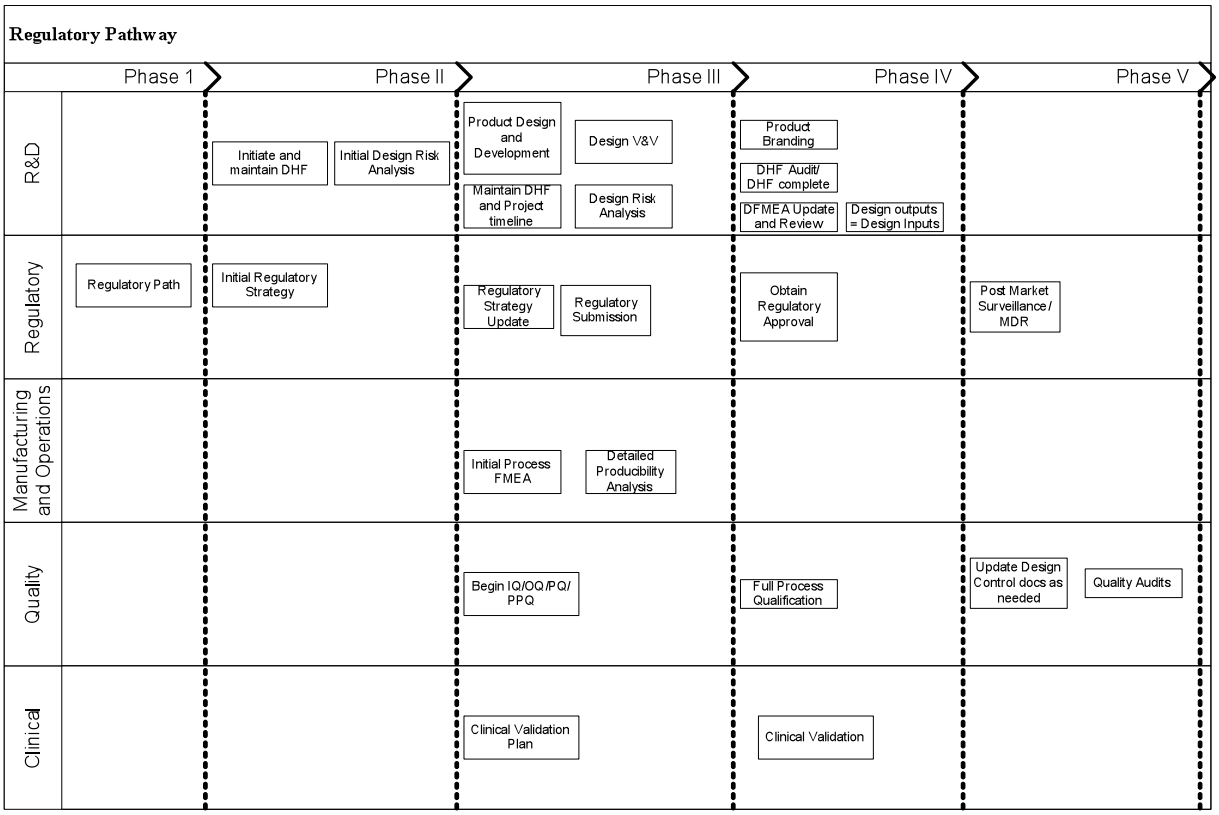


Table 4Regulatory Steps and Decision Points in PDLC

Phase 1 / Gate 1 – Initiation, Opportunity and Risk Analysis	
Activity	Develop a Regulatory strategy
Decision point	Is project risk from a regulatory perspective acceptable?
Phase 2 / Gate 2 – Formulation, Concept and Feasibility	
Activity	• Develop Design input (from user) e.g., intended use of the device, Testing requirements (i.e., strength and load-bearing requirements), biocompatibility requirements, functional requirements and physical requirements (i.e., size, material, packaging, sterilization, environmental compatibility, and appearance) (Teixeira, 2003). • Evolve Regulatory strategy. Considerations are made regarding which regulatory path to pursue (i.e., 510(k) vs. PMA) and whether or not clinical studies will be required. • Develop Initial regulatory plan • Design inputs approval / Identification of target specifications
Decision point	Is initial regulatory plan established and approved? Are inputs defined and approved and can development begin based on inputs?
Phase 3 / Gate 3 – Design and Development, Verification and Validation	
Activity	• Develop V&V test matrix, including product testing and preliminary performance testing, biocompatibility testing, and durability / longevity testing, bioburden, sterilization, cleaning, Clinical studies, mating part functional tests, exposure / environmental testing, or packaging / ship testing. • Submitting Design and test data to FDA for review and regulatory approval. • Create Verification and validation (V&V) trace matrix • Create and approve Verification protocols, perform testing, Create and approve reports • Complete Regulatory submission • Update trace matrix.
Decision point	Do design outputs properly satisfy all design inputs? Is device ready for regulatory submission?
Phase 4 / Gate 4 – Final Validation, Product Launch Preparation	

Activity	• Finalize Material specifications, packaging drawings, and marking and labeling specifications.
	• Assure design outputs satisfy inputs (Trace)
	  • Validation testing shows that the device conforms to user needs & requirements.
	  • Verification testing shows that design outputs satisfy design inputs.

Decision point	Is device ready for commercial launch from regulatory clearance perspective? Is device ready and cleared for launch?
Phase 5 – Product Launch and Post-launch Assessment	
Activity	Perform Design History or Quality Audits Gather and assess Post Production Feedback and take necessary actions
Decision point	Is product performing as intended?

Each product development project is usually driven by a core team dedicated to a specific product line (Linehan, Pate-Cornell, & al, 2007) . Therefore implementation of workflow through a product development model in a project by project fashion, Figure 11, by multiple teams in parallel can lead to duplication of efforts. As each team works through the process, they are working on the same or similar deliverables such as packaging validations or trace matrices, etc. Not only are they re-inventing the wheel within each team, they are producing these like deliverables with variability since each product team writes and produces deliverables to the level of the team's skills and core competencies.

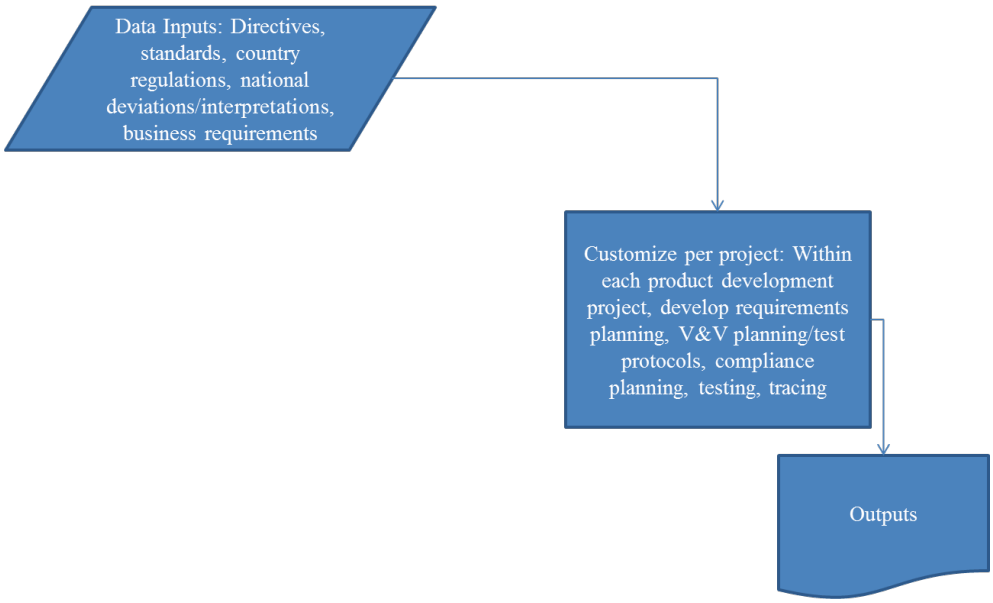


Figure 11 Project by Project Approach

While there are expected activities, resulting deliverables, and defined decision points for the regulatory pathway in the current product development model, a challenge with the implementation of this model continues to be the determination of the *appropriate* level of evidence required to *demonstrate* safety and effectiveness and this challenge is compounded by the variability created using the project by project approach.

7.3 Feedback Loops

In the current model, the development path is rarely smooth because of the many challenges and complexities associated with medical device design and development, including a changing regulatory environment and the lack of any formalism in the process. Within and after each phase of the development process, there are decisions

that are made. Design teams within medical device companies often realize obstacles along the development path from concept to launch, and into post-market surveillance at these decision points. It is at these points where there are many potential feedback loops, and conflicting objectives.

This section demonstrates reasons for iterative Regulatory loops that frequently occur along the device development pathway. The iterations presented are based on responses from the device experts interviewed as part of the Stanford BioDesign study (Linehan, Pate-Cornell, & al, 2007), the authors experience, experience of colleagues, and interactions with independent and FDA auditors. Brief examples and explanations are given for some typical iterative loops.

A regulatory loop often occurs when making the decision whether the device outputs properly meet device inputs, if the device is ready for regulatory submission or cleared for launch, and/or if the device is functioning as intended in the field.

Failures at these decision points could happen for many reasons. Specific to regulatory compliance, a test methodology may not originally have been adequate in the protocol, or testing does not meet standards requirements. This may be realized internally before a submission is made, after a submission has been made to a regulatory agency, or in worse case, after the product has been released to the field.

7.3.1 Decision – Do outputs meet inputs

Internally, for example, Regulatory is not a typical participant in the V&V testing. But in many cases, the engineers are not completely familiar with requirements

of the regulations, especially if the product standards incurred a recent revision while the company's product was in development. Regulatory may perform a final trace review, or during the consolidation of the submission, may learn that standards requirements were not satisfied hence driving product development back to an earlier stage in the process.

7.3.2 Decision – Is device ready for submission

More likely, however, after the regulatory submission is made to the FDA or to an international regulatory agency, the regulatory agency responds to the company. The FDA, for example, evaluates the evidence submitted to support the claim of Substantial Equivalence or Reasonable Safety and Efficacy, not the product design. It is common for the regulatory agency to respond to a company's regulatory submission with questions regarding test results and test methodology which are usually driven by regulatory standards. For example, the submission for a sterile medical device must include packaging data. Without that section the PMA would be considered unfilable, and returned. When this occurs, additional verification testing must frequently be performed in response to the inquiry. The Regulatory Agency will then either deny or grant clearance or ask additional questions or conditionally grant approval with the request for further testing. If regulatory clearance or approval is not granted, a re-design may be required (Linehan, Pate-Cornell, & al, 2007).

7.3.3 Decision – Is device functioning as intended

Sometimes, weak internal controls, or an inadequate regulatory review, release products to the field for customer use. However, design control deliverables continue to remain active throughout the life of a medical device. If a design flaw is detected following release to the field, for example, product is returned to the company with tears in the packaging impacting the sterile barrier, or product causes a shock to the patient when it wasn't supposed to, or labeling is inadequate in the product instructions for use, etc., the device may require recall or, possible total redesigned, depending on the severity of the issue, which may need to loop all the way back to design and development.

Likewise, in a less serious case, an internal design audit may find that a particular requirement was never met, but was never caught by an agency. This may or may not impact safety of the device, but is likely to impact regulatory risk when the company is audited by the outside agency. This may also send development back to the design and development phase, or somewhere within the development path depending on the situation.

All of these looping scenarios are depicted below in Figure 12 and can occur several times throughout the development lifecycle.

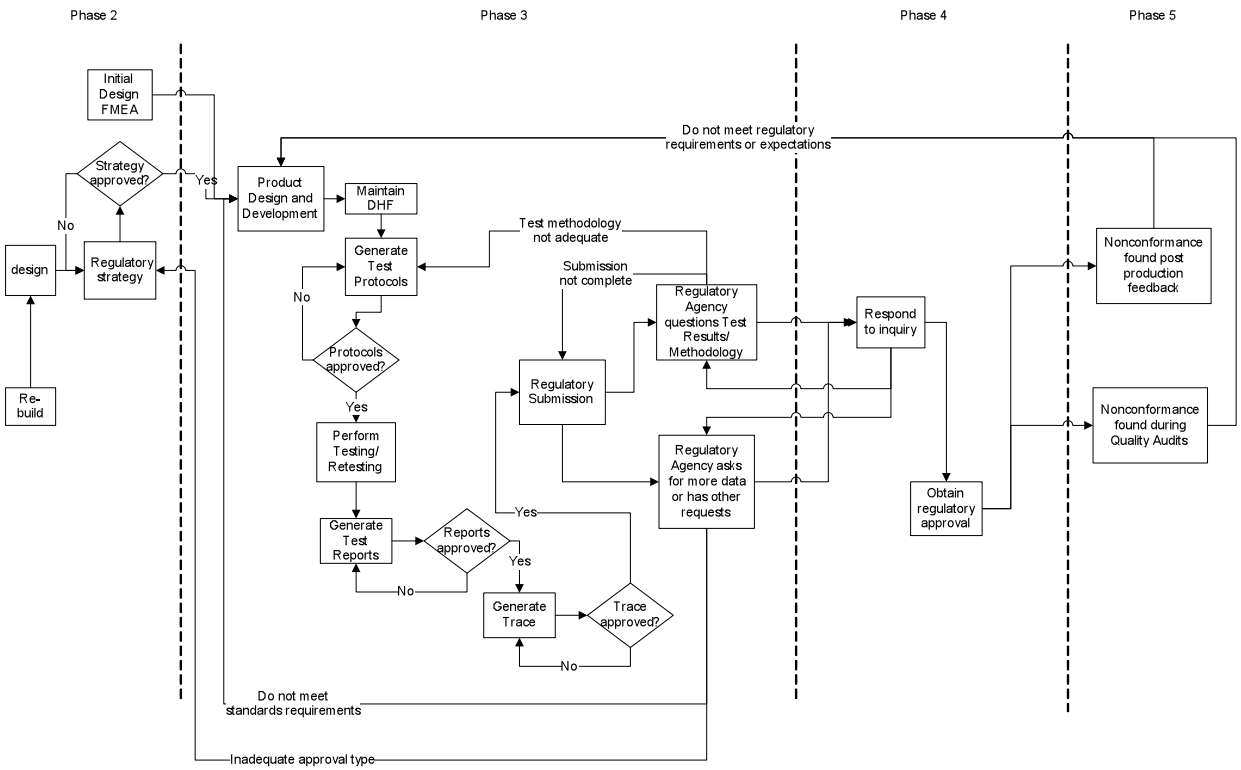


Figure 12 Iterative Loops

7.4 Proposed Model

As mentioned above, a challenge with the implementation of the current model is determining levels of "appropriateness" for "demonstrating" safety and effectiveness as well as how to reduce the number of iterations in the looping scenarios. "Appropriate" in the medical device industry is typically defined within standards and regulations or as part of the current "regulatory tolerance". Likewise is "safety and efficacy". Therefore application of a framework, Figure 13, geared to systematically manage regulatory information in a product development process will constitute a major advantage.

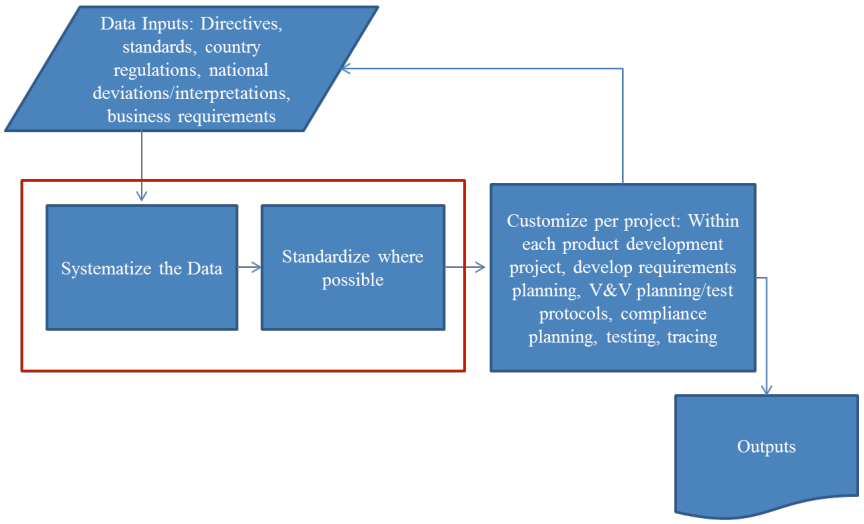


Figure 13 ADBP Compliance Framework

The proposed model in this section, Figure 14, is a high level model created by applying the Compliance Framework that was developed using the derived Axiomatic Design for Business Process (ADBP), to the systematic implementation of regulatory activities within the product development process.

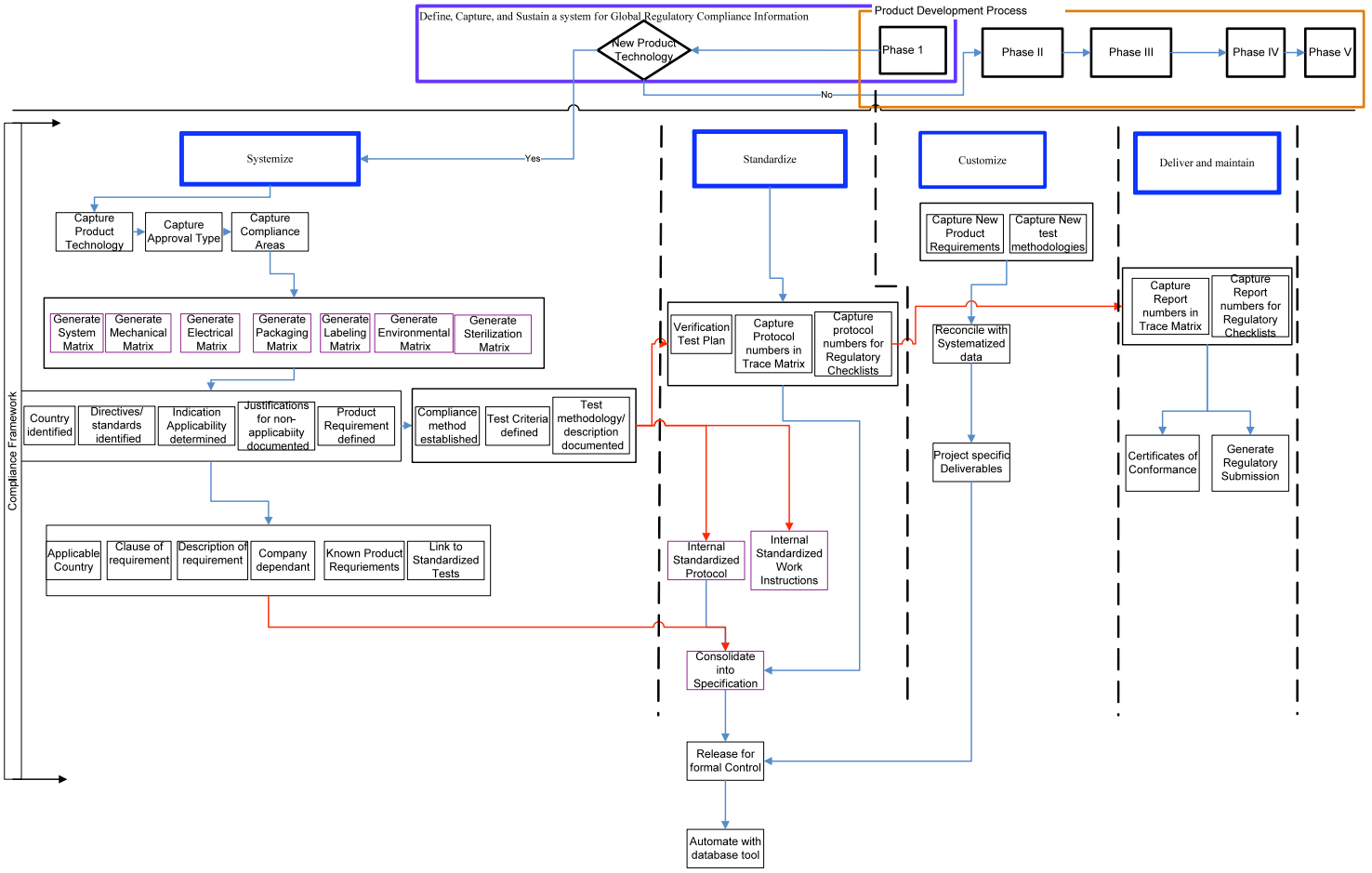


Figure 14 Applied Compliance Framework

This model shows the product development process across the top. This is the current product development process in which the implementation of the framework will integrate. Sections are separated by the dotted lines. Within the blue, bold lined boxes are the functional or Operational Requirements (OR) defined as part of the systematic ADBP design solution that describes “what the process does”:

OR1 Systemize the approach for compliance requirements

OR2 Standardize the approach where possible

OR3 Customize the information for specific project

OR4 Deliver and maintain compliant products for regulatory approvals for new product, new geographies, new indications, changes to regulatory environment

OR5 Define, Capture, and Sustain a system for Global Regulatory Compliance Information for Product Approvals

The detail below each Operational Requirement are boxes that represent the Instructional and Deliverable Requirements that were generated while working through the domains of ADBP. All together, these requirements make up the Compliance Framework and the model shows the overall implementation of the framework as an operational concept. It starts with "Systematizing" by gathering inputs from worldwide directives, standards, national legislation, and country import/export requirements that are applicable to the organizations devices, as well as gathering requirements from the organization's needs and historical development efforts such as risk management files.

Then tools would be initially developed as part of systematizing the information captured in controlled documents or databases. Deliverables or tools will be generated one time, by a knowledgeable resource, who will sustain this information as part of on-going information management. They can then be introduced into the product development process for each product type. Then this information, in the form of staged deliverables such as standardized protocols inherently traced to the regulations, or trace matrices or V&V plans for a given product type, or regulatory plans, etc., would be used by the teams to customize for a specific project. The individual project teams would use

these tools, then customize the data for a particular project based on the delta of their new product customer requirements. This delta is then captured back into the tools section of the framework as a matter of sustainability. Since this sustainability is part of the framework the data will be inherently maintained in the changing regulatory and competitive business environments.

7.4 Conceptual Example

To demonstrate the significance and value of this process, it will be applied to a limited example (one regulatory area and one product activity) of a strictly regulated, Class III device sold internationally that is governed under, in part, the Active Implantable Medical Devices Directive and the Packaging Waste Directive. Most products would require even more complex procedures with more interactions and feedback loops. Hence, if the new process can be shown to be significant and valuable for this example, it would be multiplicatively more significant for the more complex product processes. These will be considered below.

Per the Medicines and Healthcare Products Regulatory Agency (MHRA), examples of these types of Class III devices include:

1. implantable cardiac pacemakers
2. implantable defibrillators
3. leads, electrodes, adaptors for 1. and 2.
4. implantable nerve stimulators
5. bladder stimulators

6. sphincter stimulators
7. diaphragm stimulators
8. cochlear implants
9. implantable active drug administration device
10. catheters, sensors for 9.
11. implantable active monitoring devices
12. programmers, software, transmitters.

The AIMD covers the placing on the market and putting into service of 'active implantable medical devices' (AIMDs) (www.MHRA.gov). The Packaging and Packaging Waste Directive defines essential requirements for packaging to be considered recoverable. In the project by project approach, each team working on a product would have to show how they meet the requirements in these directives as they pertain to packaging. This results in the development of a protocol, implementation of that protocol, and development of a report. Both the protocol and the report would need to go through an iterative loop to review and approve the documents. In this proposed model, a generic protocol would be developed and inherently traced to the regulations. A partial example of a generic protocol might be as shown in Table 8. This would be a comprehensive protocol inherently traced to all applicable requirements outlined in the standards and internal documents, and would be written, reviewed, and approved once, and available for each team to use. This removes the effort for each team to generate the protocol and cycle it through the review and approval process. If any deviations are required from this protocol, they would be documented in the report. The regulatory

compliance engineers, for example, would be responsible for sustaining this protocol with updates to the standards, regulatory tolerance, or internal requirements. Using this standardized protocol will reduce variability in the required testing, ensure that the teams will be compliant to current requirements and give the teams back time they would have spent on generating, reviewing and approving their individual protocols.

Table 5 Partial Example of a generic protocol for Packaging Compliance

<table>
<tr><th colspan="2">Methods and Procedures</th></tr>
<tr><td>Pre-conditioning</td><td>The following preconditioning steps (if appropriate) shall be performed for the sales pack and sterile pack before subjecting the product to any functional testing.

Environmental conditions – EO Sterilant exposure

(ISO 11607-1:2006 Para 6.3.4)
Purpose
The purpose of this preconditioning is to ensure that the sales and sterile packaging can withstand effects of EO gas during sterilization.

Applicability
This test is applicable to all sales and sterile barrier systems that are terminally sterilized.

Method
The product will be sterilized the maximum number of times allowed per the product specification using the regular production EO sterilization cycle
The package shall be visually inspected for any signs of fogging, tearing, cracking or degradation and any discrepancies will be documented.

Suggested data collection template
<table><tr><td>Sample No.</td><td>Any fogging, tearing, cracking or</td></tr></table></td></tr>
</table>

Sample No.	Any fogging, tearing, cracking or degradation

Environmental conditions – Humidity

(EN 11607-1:2007 Para 4.4.3)

Purpose

The purpose of this preconditioning is to ensure that the sales packaging and sterile barrier system can withstand effects of humidity in transit or normal conditions.

Applicability

This test is applicable to all sales packaging and sterile barrier systems.

Method

The sterile barrier system will be placed in a temperature and humidity controlled oven and will be exposed to a temperature of (23 ± 1) ° C and a relative humidity of (50 ± 2) % for a minimum of 24h.

The packaging shall be visually inspected for any signs of fogging, tearing, cracking or degradation and any discrepancies will be documented.

Suggested data collection template

Sample No.	Any fogging, tearing, cracking or degradation

Based on the author's experience, and confirmed in interviews with other experts in the medical device field, Table 9 below represents a fair estimate of time and resources to create and cycle through a review/approval for a protocol.

Table 6 Estimate

Activity	**Time**	**Resources**	**Iterations**
Generate V&V protocols	8 -32 hrs	3 Individual Contributors	
Review/ Approve V&V protocols	1-4 hrs each per resource	3 Functional Area Management	3 times

Assuming an individual contributor makes $100,000, approximately $48 per hour, and functional management makes $120,000, approximately $58 per hour, and using Equation 5 below, we can estimate the cost savings after first time use related to implementing the framework, systematizing the requirements data, standardizing the data, then implementing the model.

$$\sum \text{Activity} * (\text{average time in hours}) * (\#\ \text{Resources}) * (\ \text{hourly rate}) * (\#\ \text{of iterations})$$

Equation 5 Cost for Conceptual Example

Calculating this equation, we get:

(1 protocol*20 hours * 3*$48 * 1) + (1 review/approve * 2 hours * 3*$58 * 3) =

($2880+$1044)) = $3924

In this simple, conceptual example alone, there is a cost savings of almost $4000 by the second time the process is used and each time thereafter. Additionally, there is a reduction in compliance risk since the standardized protocol is inherently traced to the requirements, a reduction in variability since all teams will be following the same protocol, and a time savings of approximately 80 hours (60 hours plus 18 hours). Multiply this across multiple regulatory standards, multiple regulatory activities, and multiple product teams, and the benefits would be exponential.

7.5 Comprehensive Analysis

7.5.1 Time and Resources

The simple example described above was for only one regulatory area and one Product Development activity. The Stanford Study describes many activities that may have impact due to the regulatory pathway throughout the product development process. To better demonstrate the greater value of the proposed model, it is important to understand the time, resources, and number of iterations these activities require. Time frames for these efforts within the PDLC were obtained wherever possible from the Stanford BioDesign Study on Product Development Models (Linehan, Pate-Cornell, & al, 2007). According to this study, the lifecycle of the first four phases of a medical

device development, product concept to product launch, can range anywhere between 2-6 years with design and development ranging from 1-2 years.

Estimates were also made based on the authors experience and confirmed in interviews with other experts in the medical device field. Therefore, it is with good judgment that the following time frames depicted in Table 7 for certain efforts within the development process can be made.

Table 7 Time and Resources

Activity	Time range	Resource Range	# of iterations
Develop Regulatory strategy	16-40 hrs	3-5 Individual Contributors	
Approve Regulatory strategy	2-4 hrs	3-5 Functional Area Management	2-3 times
Product Design and Development	1-2 yrs	Multiple	
Generate V&V protocols	8 -32 hrs	2-3 Individual Contributors	
Review/ Approve V&V protocols	1-4 hrs each per resource	2-3 Functional Area Management	2-3 times
Implement V&V testing	3-9 months	2-6 Individual Contributors	
Generate V&V reports	8-40 hours	3-4 Individual Contributors	
Approve V&V reports	3-40 hrs per	3-4 Functional Area	

	resource	Management	
Develop initial risk assessment	16-32 hrs	4-5 Individual Contributors	
Develop final risk assessment	16-40 hrs	4-5 Individual Contributors	
Review Approve final risk assessment	3-8 hrs per resource	4-5 Functional Area Management	1-5 times
Develop initial trace matrix	23-30 hrs	4-5 Individual Contributors	
Develop final trace matrix	40-100 hours	4-5 Individual Contributors	
Review/Approve trace matrix	2-20 hours per resource	4-5 Functional Area Management	1-5 times
Perform DHF Audit	16-80 hrs	1-2 Individual Contributors	
Obtain Regulatory Approval	110-265 days		2-30 times

The effort with the greatest single time commitment relates to obtaining regulatory approval and this happens towards the back half of the process. For product review in the United States, the FDA regulations provide a statutory timeframe of 180 days to review the PMA and make a determination on its acceptability (FDA). Because of frequent requests for additional information, the review time for a PMA can, in reality, often be significantly longer than 180 days. According to experts in the field, requests for additional information are due to various reasons, some of which include:

- where to find verifications
- system information is missing or does not matching labeling, instructions for use, documentation, application, certificate
- not following clinical data guidelines
- standards non compliances

7.5.2 Example

Now that we have time and resources for certain activities, we can walk through a more comprehensive example. Using the same basis as for the conceptual example above, we take one of the Class III devices listed by the MHRA that is sold internationally and governed under specific Directives. For this type of device, a product team would need to perform, in part, mechanical, electrical, software, packaging, sterilization, biocompatibility, labeling verifications. Of course there are many other activities as seen in the current product development model such as regulatory plans, risk assessments, and the regulatory submission among others. There would also be the need to develop deliverables such as an Essential Requirements Checklist and a trace matrix to name a few. For the simplicity of this example, let's look at some activities associated with verification testing , reporting, and trace matrices as depicted in Table 8 below.

Table 8 Implant Development Project by Project with Current Model

	Description	***No. of protocols/ initial deliverable***	***No. of reports/ final deliverable***
Mechanical/ Electrical	mechanical verification	1	1
	electrical verification	1	1
Software testing	Charging	1	1
	Communication and Stimulation	1	1
	60601-1-4 compliance	1	1
Packaging	Ship test	1	1
	Shelf life/packaging	1	1
Sterilization	Sterilization validation report	1	1
	ETO residuals	1	1
	Bioburden	1	1
Biocompatibility report	Cytotoxicity	1	1
	Biocompatibility testing	1	1
Labeling verification	Manual verification	1	1
Essential Requirements Checklist	ERC	1	1
Tracing for external standards to product requirements and to testing	Housed in the trace matrix	1	1

Total number of deliverables		***15***	***15***

Applying the proposed Compliance Framework would reduce the number of protocols or initial deliverables that would be required as depicted in Table 9 below. Having applied the Compliance Framework and front loading the product development cycle as in the proposed model for this example would have resulted in the generation of standardized protocols and trace matrices or databases from the systematized data that would be in place for the teams to use. Any deviations to the protocols would be captured in the "customized" reports with rationale. There would also need to be the "customized" data specific to the product under development such as a mechanical verification specific to the design of the new product.

Table 9 Implant Development with Compliance Matrix

	Description	***No. of protocols/ initial deliverable***	***No. of reports/ final deliverable***
Mechanical/ Electrical	Mechanical/ electrical per 45502-1	0	1
	Mechanical electrical testing per delta internal requirements	1	1
Software testing	Software testing per generic internal requirements	0	1
	Software testing per delta internal requirements	1	1
Packaging	Packaging verification per 11607-1	0	1

Sterilization	Sterilization verification per EN 556-1	0	1
Biocompatibility report	Biocompatibility testing per 10993-1	0	1
Labeling verification	Labeling verification	0	1
Essential Requirements Checklist	Essential Requirements Checklist	0	1
Tracing for external standards to product requirements and to testing	Tracing for external standards to product requirements and to testing	0	1
Total number of deliverables		***2***	***10***

By comparing the number of deliverables from Table 12 to those in Table 13, it can be seen that by applying the proposed Compliance Framework, the number of deliverables in this example went from 15 initial documents or protocols to 2 and from 15 final deliverables or reports to 10.

Once again, time frames for these efforts within the PDLC were obtained wherever possible from the Stanford BioDesign Study on Product Development Models (Linehan, Pate-Cornell, & al, 2007). Estimates were also made based on the authors experience and confirmed in interviews with other experts in the medical device field. Therefore, it is with good judgment that the following time frames depicted in Table 10 for certain efforts within this example can be made.

Table 10 Summary Data for Example

	Deliverables		Ranges		
	Current Model	**Proposed w/ Framework**	**Time**	**Resources**	**Iterations**
Total number of verifications-protocols	***13***	***2***	8 to 32 hours	2-3 people from R&D, mnfr engr, qual	
Document Review/Approval	***13***	***2***	1-4 hrs each	2-3 functional mngt	2-3 times
Implement Testing			3-9 months	3-6 people from tech services/Marketing, mnfr engr, qual, reg, clin, R&D	
Total number of verifications-reports	***13***	***10***	8-40 hours	3-4 people from mnfr eng, clin, reg , qual, R&D	
Document Review/Approval	***13***	***10***	3-40 hours	3-4 functional mnmt	
Total number of traces- initial	***2***	***0***	20-32 hours	4-5 people from Qual, R&D, Clin, Marketing, Mnfr Engineering	
Document Review/Approval	***2***	***0***	2-20 hours	4-5 functional area mngt	1-5 times
Total number of traces- final	***2***	***2***	40-100 hours	4-5 people from Qual, R&D, Clin, Marketing, Mnfr Engineering	
Document Review/Approval	***2***	***2***	2-20 hours	4-5 functional area mngt	1-5 times

I developed a cost model, below, for working through a product development effort. Where equation 4 in the conceptual example used averages for time and resources, equation 5 represents the general equation to be used with any data.

$TC = \sum_{f=1}^{N} A_f * T_f * R_f * C_f * I_f$

Equation 5 Total Cost

Where:

TC =Total Estimated Cost

f =actual data for given example

N =Number of activities

A = Product Development Activity influenced by the regulatory pathway

T_f = Time to complete activity

R_f =Number of resources required to complete activity

Cf = Hourly rate for people performing the effort

I_f =Number of iterations typical for a given activity

In the case of this example, there are ranges in the table. Focusing on the minimum and maximum of these ranges, we get a TC min and TC max. This will show the range of costs and time that can be saved in this example alone. Plugging in the data associated for this example, we get the following calculations:

TCmin Current = (13*8*2*$48*1)+(13*1*2*$58*2)+(13*8*3*$48*1)+(13*3*3*$58*1) + (2*20*4*$48*1)+(2*2*4*$58*1)+(2*40*4*$48*1) +(2*2*4*$58*1) = 9984+3016+ 14976+ 6786+ 7860+928+ 15360+928= $59,838

TCmin Proposed = (2*8*2*$48*1)+(2*1*2*$58*2)+(10*8*3*$48*1)+(10*3*3*$58*1) + (0*20*4*$48*1)+(0*2*4*$58*1)+(2*40*4*$48*1) +(2*2*4*$58*1) = 1536 + 464+ 11520+ 5220+0+0+15360+928= $35,028

TCmax Current = (13*32*3*$48*1)+(13*4*3*$58*3) + (13*40*4*$48*1) + (13*40*4*$58*1)+(2*32*5*$48*1)+(2*20*5*$58*5) + (2*100*5*$48*1) + (2*20*5*$58*5)= 59904+27144+99840+12064+15360+58000+48000+58000= $378,312

TC max Proposed = (2*32*3*$48*1)+(2*4*3*$58*3) + (10*40*4*$48*1) + (10*40*4*$58*1)+(0*32*5*$48*1)+(0*20*5*$58*5) + (2*100*5*$48*1) + (2*20*5*$58*5)= 9216+4176+76800+92800+0+0+48000+58000=$288,992

These calculations show a cost savings after applying the Compliance Framework in this example ranging from $24,810 - $89,320. This example did not include many activities such as the risk activities and the regulatory submission where a great gain would be achieved.

Also, using standardized protocols reduced variability in the required testing, ensuring that the teams were compliant to current requirements and gave the teams back time they would have spent on generating, reviewing and approving their individual protocols. Having the trace matrices already created and in compliance matrices or a database also reduces the time it takes a team to generate these documents project by project while ensuring the appropriate regulations are followed as well as the current

regulatory tolerance. This time savings can be critical in this highly competitive medical device market place.

Front loading the product development process as in the proposed model will ultimately contribute to improving efficiency throughout the product development process, from development through global regulatory approvals, while inherently and efficiently remaining compliant during all phases of the development and as well as consistently demonstrating "safety and effectiveness". This analysis was for a single product and a partial cycle with only 15 activities. A typical moderate size company may have 4 or more products under development at any given time and each having at least three times as many, or more, activities for each team that will be influenced by the regulatory path. There would also be the post production feedback that each product goes through upon product release to the market. Applying this to the savings shown above could result in savings of millions of dollars, shorter approval cycles, and less risk to the company and greater compliance to develop safe and effective devices. In addition to the financial savings achieved utilizing this process, the formalism of the process includes a far more requirements traceable process for design and regulatory compliance, with the ultimate goal of safety for the patient.

Chapter 8

CONCLUSION AND FUTURE WORK

8.1 The Problem

In the biomedical industry, innovation is key. But you can't have innovation without safety, effectiveness and regulatory compliance. And you can't always comply to regulations and get to market as quickly and affordably as you'd like. Many companies tend to look at regulatory compliance as a sort of necessary evil that ultimately challenges efficiency throughout the product development process. Yet disaster, in the case of noncompliance, may result in loss of product certification, no regulatory approval, inability to sell the device, or worse yet, harm to a patient. There is a real challenge, then, to striking the balance between compliance and pushing product through the pipeline in a way that secures the competitive advantage of being first to market.

The problem is that the business (quality system) procedures that are responsible for defining the operations surrounding designing, developing, building, and selling this innovative product have typically been only regulation driven, leading to significant inefficiencies resulting in unsatisfactory business operations, slower times to market, poorer product quality, and increased costs. The regulations, however, are only part of the requirements for an optimal business 'process'. Another and arguably more significant part in this effort is understanding and incorporating the requirements for the

business operations as a true system, including the needs from *all* of the stakeholders involved in that process, including the implementers of the process as well as the global regulators.

Typically, there are few processes developed using true design methodologies that provide some structure and a systematic approach to development. Business, or quality system, processes are not typically designed with the same robustness with which the product is designed. It is meeting the totality of the stakeholder requirements within the process that ultimately yields quality. Yet still, the paradigm is hard to shift and process design becomes an exercise in subjective opinion and such other types of ephemeral "tools" from when processes, or more so the procedures that define the process, were defined in a vacuum and primarily to meet regulations. So business (quality system) processes are still often designed without consideration of all stakeholders.

Business processes cannot be created in a vacuum and one size does not fit all. So each manufacturer has the responsibility to establish requirements for the type of product they develop, the countries in which they intend to sell their product, and the people who will be implementing the process. Additionally, they must determine the most value-added operational concept that can implement these processes.

In the governing biomedical Directives, there are required standards that govern process including requirements surrounding risk and safety. Often, there is no dedicated resource to define, interpret, and educate the company in a consistent and accurate way on which product standards, clauses, test criteria, etc. are applicable for the specific technology, from around the world. This may be left up to the working engineers on the

project team. Hence, engineers typically work to comply with these standards in a project by project approach. This increases the adverse potential for complexity, inconsistency, inaccuracy and inefficiency in process and documentation, such as; with requirements management, verification test definitions, protocol development, and regulatory measures for each project of the same product type. They may take a best guess at which product regulations are applicable to the technology being developed, based on a past effort, and usually only as it relates to the United States and the European Union. Many times, the project teams don't find out until either late in the development cycle (after a regulatory submission rejection) or after not being able to sell into a country, which standards and/or national legislations are applicable, or more critically, what the current interpretation and expectation is of the standard requirements. This operational strategy delays the product development lifecycle due to redundant paperwork activities, rework, and redesign and increases regulatory risk to the organization, by creating complicated, variant documentation and a lack of apparent compliance to the technical product standards.

Complicating the situation is that product and process standards are influenced by a current regulatory environment and specific country interpretation or expectations of the standards and regulations that drive the needs and requirements for these types of business processes and product requirements. Even though a company designs and tests under the constraint of the standard, a specific country may wish for, or expects, verification testing, for example, to be done in their own country or by a designated lab. This is done, for example, in some Asian countries. This is not a constraint of the

standard itself, rather an expectation of that country based on the current regulatory environment.

Furthermore, the implementation of regulations and standards in the biomedical device industry has become more risk based, which is widely open to interpretation. So some regulatory requirements might constrain what functions have to be considered in a business operation or process for the regulated industry, but they do not constrain *how* to do this, whereas the "regulatory tolerance" might. In the same way, there are global product standards that can influence the product development business process. These requirements are to the process, as product requirements are to the product they produce. More complicated technology, requiring greater cross-functional involvement and more demanding stakeholder needs, leads to more complex process solutions that result in safe and effective products being developed and manufactured. These types of operational efforts are also challenged by the changing global directives, standards, and national legislation and, in turn, are challenging efficiency throughout the product development lifecycle.

Herein lays the challenge of balancing process that pushes product through the pipeline and at the same time, meeting all stakeholder and compliance requirements. The Product Development, or Design Control, process is the business process biomedical manufacturers most often try to optimize and continuously improve, not only in an effort to meet the changing demands of regulating bodies, but to meet more demanding stakeholder needs, including the regulators. Likewise, there are more challenges with competition. In effect, companies need to reduce time to market, increase product quality,

ensure organizational compliance, and decrease development costs. So the design of a business process that optimizes efforts throughout the Product Development Lifecycle can largely lead to the medical device manufacturer's success or failure.

Therefore, medical device companies are faced with redesigning how they operate from a more systematic and comprehensive manner, operating in a way that meets both the business needs of the internal stakeholders as well as new demands and requirements of regulating bodies, thus driving companies to improve their business operating processes or tools, as well as needing to develop the operational framework for these processes.

Consequently, there is a recognized and critical need to know and manage this global regulatory knowledge in a way that will contribute to improving efficiency throughout the product development process, from development through global regulatory approvals, while inherently and efficiently remaining compliant during all phases of the development and as well as consistently demonstrating "safety and effectiveness".

The real goal of any overall design effort is to optimize the performance of the system (Hintersteiner, 2000). Consequently, the unfulfilled need, fulfilled by this research, to find or develop a superior design technique or methodology, use this methodology to develop a design solution for a "process" or system of activities, which surrounds regulatory compliance, where regulatory compliance is not just a deliverable of the product development process, but a driver to its optimization. This needed to result in improving efficiency throughout the product development process, from development

through global regulatory approvals, while inherently and efficiently remaining compliant during all phases of the development and as well as consistently demonstrating "safety and effectiveness" with the ultimate goal of balancing safety for the patient, and being first to market to secure competitive advantages.

8.2 Axiomatic Design

While there are many less rigorous ways to design and develop a process, using a rigorous design methodology offers the type of innovative solution to this challenge that when implemented, will offer a medical device organization a real competitive advantage. There are many different types of design approaches and tools, some based on the premise of others, used in design such as House of Quality, Statistical process control (SPC), Taguchi, Altshuller inventive Problem Solving, and such. Axiomatic Design is applicable to all designs, however. It deals with principles and methodologies rather than with algorithms and tools. Robust Design is based on the two axioms that govern the analysis and information minimization in the design challenge. To be valid, all approaches must satisfy the design axioms. Altshuller satisfies the design axioms, but is used primarily to derive Design Parameters consistent with Constraints based on the rule of "contradiction". Taguchi, for example, is valid only on design that satisfies the independence axiom. House of Quality is used to improve an existing design by incorporating customer attributes in the functional requirements. Most critically, these approaches supply a method for checking or improving an existing design solution. (Suh, May 2001)

This research aimed to develop a novel approach to the design challenge in the regulated industry of balance between compliance and safety and effectiveness with getting product to market quickly to secure competitive advantages that come with being first to market. Axiomatic Design offers a method steeped in rigor and a systematic approach to develop a truly creative, innovative and robust design solution without bias by preconceived solutions.

Therefore Axiomatic Design (AD) provided the basis for the innovative solution generated in this research. It uses matrix methods to systematically analyze the transformation of stakeholder needs into functional requirements, design parameters, and process variables. It integrates scientific principles and system engineering tools into the design process, in order to improve design activities. The formalities of the AD process were desired to represent a potential solution to the design challenge, however, it was determined that classical AD has some limitations with respect to these regulated industries, as well as other industries which have similar business processes (Easton D. , 2010)

8.2.1 Axiomatic Design Limitations

While AD is a robust design methodology that may be used to create such designs as software, manufacturing processes, systems, or organization, applying the AD methodology to the design of a Business Process is complicated and confusing as the methodology is presently defined. Suh describes the design world to include four domains that create demarcation lines between the four different design activities. While

AD Advances and Applications provide examples using AD for a business/organization or a process (manufacturing), it does not for a Business Process. The text describes, for example, that the Process Variables in the Process domain for a "business" might represent the human or financial resources. The Process Variables in the Process Domain for a manufacturing process might specify the manufacturing process variables that can produce the design parameter (Suh, 2001). Neither of these is applicable to designing the "product" of a "Business Process" in a regulated industry. It becomes complicated and confusing, when trying to develop a total design solution for a Business Process, once one gets into the Process Domain.

Specifically, the product development process in the regulated medical device industry is unique from other development processes in that it must incorporate the "regulatory tolerance" for the changing global regulatory interpretations and expectations. "Regulatory Tolerance" is a term introduced and defined by this author as "a variable regulatory expectation, interpretation, or guidance, in an individual country or group of countries, based on the current regulatory environment of that country". Additionally, business Process in a regulated industry should consist of procedures, instructions, and records or deliverables. But for the AD axioms to hold true in the Business Process design, the AD domains required substantial modification.

Undoubtedly, there is advantage in using a design methodology such as Axiomatic Design to develop an innovative solution to Business Process Design which may offer a biomedical device organization a real competitive advantage. But the confusion using the methodology as defined today lends itself to perceived complexity,

the inability or more critically, the disinterest to use the methodology for the application of Business Process design, albeit the robust design approach and the axiomatic principles would be advantageous to designing an innovative Business Process.

Therefore, for this type of industry, there was a need to adapt and expand the AD methodology and expand the rules of AD as it applies to developing an uncoupled design for a cross functional process. This research has introduced the required extensions, modifications and clarifications of the design methodology when developing a Business Process to solve the aforementioned problems.

8.3 Axiomatic Design for Business Processes (ADBP)

The AD methodology was adapted and the rules were expanded into ADBP which has introduced the required extensions, modifications and clarifications of the design methodology when developing a Business Process in the regulated industry. These included:

- Unique and significant modifications to AD Technique, to be used for creation of business processes;
- Modifying the Design Axioms to address a cross-functionality of process;
- Development of new concept – Regulatory tolerance
- Development of a significant and novel methodology to overcome regulatory tolerance by adding a concept of a Regulatory Lens between domains.

8.3.1 ADBP: Domains

In AD, the Customer Domain consists of the customer needs. The Functional domain specifies the functional requirements and constraints necessary to satisfy the customer needs. The physical domain is the domain in which design parameters are chosen to satisfy the functional requirement. The process domain specifies the process variables that can produce the design parameter.

The fundamental concept of Axiomatic Design for Business Process is that there are four domains in the design world for a business process in the regulated industry: Customer, Operational, Instructional, and Deliverable.

The Customer Domain remains the same and is described by the needs of the stakeholders for the process.

The Functional Domain is renamed the Operational Domain [OD] and is now described by the transformation of customer needs (CN's) into a high-level set of functional or Operational Requirements (OR) that describe "what the process does" to satisfy those CN's. The Operational Requirements become more specific consisting of the system based Standard Operational Requirements and operational constraints of the Business Process.

The Physical Domain is renamed to the Instructional Domain [ID] to better reflect the design activity that occurs at this stage of designing a Business Process in a regulated industry. The Instructional Requirements do not really reflect the design parameters of the Business Process itself, rather they describe the translation of the high-level operational functions to the specific Instruction necessary to complete the standard

operation. Therefore, this domain consists of the work instruction or business process steps in an instruction that supports the operational requirements in a procedure.

The Process Domain was also modified to be the Deliverable Domain. The Deliverable Domain describes the translation of instructional requirements into resulting deliverables or outputs needed to objectively show evidence of implementing the instructional requirements.

8.3.2 ADBP: Design Axioms

The common elements of all good designs remain the same. Therefore, in ADBP, the same fundamental axioms, albeit with some revision to their definition, govern the analysis and decision making process in developing high quality product or system designs.

1) Independence: This axiom maintains and promotes the independence of various operational requirements, such that instructions may be modified to satisfy a particular operation without affecting the overall operational framework.

2) Information: This axiom states that the information content of alternative designs should be minimized, thus maximizing the success of the design.

The application of the axioms forced prioritization of requirements. Designs which do not satisfy the Independence Axiom are called coupled. Designs which satisfy

the Independence Axiom, in the case of ADBP, are called decoupled. This is a major difference between AD and ADBP. The IRs are to be independent to its immediate operational requirement, however since a business operates cross-functionally, the individual operations and instructions will integrate. It is the author's experience that this integration is often overlooked, or not fully understood, within the typical design of a business process in the regulated industry. In an acceptable design meeting the independence axiom, the IRs and ORs are related in such a way that a specific IR can be adjusted to satisfy its corresponding OR, but will impact the other ORs, as necessary, only in the case of integration points. Consequently, the order of adjusting the Instructional Requirements in a decoupled design is important.

8.3.3 ADBP: Mapping and Hierarchy, and Zigzagging

The decomposition process to transform the operations into instructions between the domains is systematically analyzed using matrix methods. The design matrix begins with a systems perspective of the process and cross references and maps the instructional requirements from the top level, the operational framework, through each domain and hierarchy.

This alternating between pairs of domains to decompose the operations to instructions to deliverables is referred to as zigzagging as it is with AD. The hierarchies represent the design architecture and the decomposition process establishes the matrix mapping between ORs, IRs, and DRs.

The decomposition between the domains is represented by a design matrix, which shows the relationships between ORs and IRs. The design matrix between the Operational Domain and the Instructional domain will be decoupled as opposed to the truly uncouple solution one might seek in pure AD. This is because each set of instructions designed in the instructional domain must work together as a system with integration points to each high-level operation in the Operational Domain. The key is to minimize these integration points to what is necessary and most simplistic for the same reasons using the AD methodology recommends gaining a truly uncoupled solution. This will still allow for independence between the instructions, but will support the instructions coming together into one overarching system operational concept.

The design matrix between the Instructional Domain and the Deliverables Domain should continue to strive for the uncoupled solution but decoupled is also acceptable.

8.3.4 ADBP: Regulatory Lens and Zigzagging

The decomposition of the IR's developed in the Instructional Domain and DR's developed in the Deliverable Domain are complicated by the current regulatory environment and specific country interpretations of the standards and regulations that drive the needs for these types of business processes.

Specifically, according to AD methodology, constraints limit the choice of design parameters. Whereas in ADBP in the global regulated industry, constraints such as those found in process standards like ISO 14971, Medical Devices- Application of Risk

Management to Medical Devices, or quality system regulations such as those found in ISO 13485:2003 might operate as a system constraint, one which is imposed by the system in which the design solution, or Business Process, must function.

The implementation of these regulations and standards in the medical device industry, though, has become more risk based. So some regulatory requirements might constrain what functions have to be considered in a Business Process for the regulated industry, but they do not constrain how to do this. Therefore moving from the Operational Domain to the Instructional Domain, the Instructional Requirements that most simply satisfy the Operational Requirements are left up to interpretation, but are still dependent on the current regulatory environment of a given country. This "interpretation" is considered to be a "tolerance" or "ambiguity" to the regulation or standard. Even if a regulatory standard is harmonized across countries, the individual country's regulatory agency may have a different expectation for how to meet the requirements.

The zigzagging process between the modified domains of ADBP, in the specific situation of designing a global Business Process in the Regulated Industry, therefore requires a further need to modify and extend the AD methodology. Key to this significant modification is the introduction of the new term "Regulatory Tolerance" which is created and defined by this author as "a variable regulatory expectation, interpretation, or guidance, in an individual country or group of countries, based on the current regulatory environment of that country". In the regulated industry, it is necessary to review and accommodate this regulatory tolerance. Learning about or addressing this

variable tolerance is often done at the later stages of the product development lifecycle, after the rejection of a regulatory submission or the unexpected inability to sell product into a specific country. Therefore, this significant and unique modification and extension of the AD methodology also includes what this author has designed as a Regulatory Lens. This Regulatory Lens is a tool that is placed between the design domains of ADBP. When decomposing requirements, it must be done through this Regulatory Lens, forcing review of applicable regulatory tolerance at the front end of the lifecycle. When there is the case of possible tolerance, one would need to bounce against this lens, opening the regulatory gate for a specified requirement. When the gate is open, zigzagging occurs as normal between the domains. When the gate is closed by the designer, the zigzagging is halted between the domains and the zigzagging bounces against the closed gate until all country's tolerance for a given requirement is addressed. Once addressed, the gate re-opens and normal zigzagging resumes through the domains. So while a requirement may be for a protocol, regulatory tolerance identifies certain expectations for the execution of the protocol, and decomposing through the Regulatory Lens requires the determination of specific tolerance for each country of interest; such as execution of the protocol must be performed in-country, or by a particular lab.

These two significant and unique modifications and extensions to the AD methodology simply and systematically addressed the interpretations of multiple countries for the same basic function resulting in the most robust global solution for the desired Business Process in this research.

8.4 Summary

Axiomatic Design is a design methodology better than others for the purposes of this type of design challenge. However Axiomatic Design had limitations for use in developing a business process in the regulated industry. Therefore it was significantly modified and enhanced to create a novel methodology, Axiomatic Design for Business Process, ADBP. To verify the significance of using ADBP in the regulated industry, it was applied to a design challenge, to create a significant business process that focused on improving the product development lifecycle by optimizing the regulatory compliance workflow through this lifecycle. The solution went beyond basic requirement management or tracing practices and resulted in more control, the reduction of risk, and a cost return on investment.

This systematic approach in ADBP to translating, prioritizing, organizing, analyzing and decision making on design requirements proved a superior tool in developing the simplest, most efficient and most compliant business process which led to the innovative and significant Compliance Framework to be used in the regulated biomedical industry.

By following ADBP, the novel and innovative solution was created in a solution neutral environment and not biased on the "ways things have always been done". The modifications and enhancements that created ADBP accounted for the cross functional nature of the business process, the regulatory tolerance see in the regulated industry, the expectations of a design hierarchy that included the overarching process, the instructions

to achieve that overarching process, the objective evidence required as part of fulfilling those work instructions and the analysis and prioritization of all such requirements.

Following this practice in this research resulted in the necessary steps of the operation being defined as well as how the operations must work together. This resulted in pulling the otherwise independent instruction up into the overarching system of operations or the Compliance Framework that proved to be a significant advantage when applied to the product development process.

To validate that the Compliance Framework is a significant approach to reduce risk and save time and money, it was applied to a subset of the comprehensive development model, the regulatory pathway through the Product Development lifecycle. The "current" process was defined based on a study of medical device development models published by the Stanford BioDesign group. Then the Compliance Framework developed by applying ADBP, which, at a high level, includes systematizing, standardizing, customizing, delivering and sustaining the regulatory information throughout the product development process, was applied to this current product development model to create a proposed model. Then, taking into account the activities developed as part of the product development process as they pertain to the regulatory work flow, the possibility for feedback loops through this process, the time, number of resources, hourly cost of those resources, and number of iterations that are typical for a given activity, the cost and time returns were calculated using a cost model also developed as part of this research.

These calculations showed a cost savings after applying the Compliance Framework in this example ranging from $24,810 - $89,320. This example did not include many activities such as the risk activities and the regulatory submission where a great gain would be achieved.

Also, using standardized protocols reduced variability in the required testing, ensuring that the teams were compliant to current requirements and gave the teams back time they would have spent on generating, reviewing and approving their individual protocols. Having the trace matrices already created and in compliance matrices or a database also reduced the time it takes a team to generate these documents project by project while ensuring the appropriate regulations are followed as well as the current regulatory tolerance. This time savings can be critical in this highly competitive medical device market place.

Front loading the product development process by applying the Compliance Framework to create the proposed model ultimately contributed to improving efficiency throughout the product development process, from development through global regulatory approvals, while inherently and efficiently remaining compliant during all phases of the development and as well as consistently demonstrating "safety and effectiveness". The validation example was for a single product and a partial cycle with only 15 activities. A typical moderate size company may have 4 or more products under development at any given time and each having at least three times as many, or more, activities for each team that will be influenced by the regulatory path. There would also be the post production feedback that each product goes through upon product release to

the market. Applying this to the savings shown by the example could result in savings of millions of dollars, shorter approval cycles, and less risk to the company and greater compliance to develop safe and effective devices. In addition to the financial savings achieved utilizing this process, the formalism of the process includes a far more requirements traceable process for design and regulatory compliance, with the ultimate goal of safety for the patient.

8.5 Future Work

This research has not only shown significance in the solution, but has also opened up many doors to future work. These include, in part, the following topics:

- Development of a commercial tool to be used in the regulated industry that generates a sustainable framework and subsequently automates various deliverables for use by regulated companies throughout the product development lifecycle.
- Simulate various scenarios for the proposed model to look for an optimal path under various real world constraints. Realizing that no single path through the model will be optimal for all applications because each different company is focused on different technologies, different countries of sale, particular organization constraints, etc. which all play into these different real world examples.

- Use of ADBP to develop a novel and significant Framework to systematically address process for Risk Management or Reimbursement strategies in the medical device industry.
- Develop a methodology to determine an optimal or near optimal path for unique variables particular to a given company and regulatory environment. This may involve the development of a tool to guide a company along a near optimal path for their environment. The development of a tool may be something that would have to be done and verified inside a company, since all competitive companies in an area hold the relevant data highly proprietary. Alternatively, a major regulatory agency, as in the FDA, may have the needed data and could provide it as part of a funded research project.
- Determine what other regulated industries could benefit from the ADBP methodology.

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