Axiomatic Design in the Biomedical Industry

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ABSTRACT

Axiomatic Design (AD) is a science and design methodology that has evolved from the technology of design. It infiltrates scientific principles into the design process in order to improve design activities. The methodology utilizes customer needs as input and produces functional requirements, design parameters, and process variables through the use of matrix methods. This systematic approach to translating the customer needs is a methodology that may be a superior tool to defining quality system process design and development in the regulated biomedical industry.

Keywords: Axiomatic Design, Quality System, Process, Biomedical

INTRODUCTION

On July 16, 2002 the Bush Administration released its National Strategy on Homeland Security. Here they defined Critical Infrastructure as "systems and assets, whether physical or virtual, so vital to the United States that the incapacity or destruction of such systems and assets would have a debilitation impact on security, national economic security, national public health or safety, or any combination of those matters." [1]

One of the thirteen sectors of the US Critical Infrastructure identified by the National Strategy on Homeland Security is that of Health Systems. The agency liaison of this sector, one with whom the Office of Homeland Security coordinates efforts to respond to threats and hazards to the Nation, is the Department of Health and Human Services. Within this department is the operating division of the Food and Drug Administration (FDA).

On March 16, 2004, the FDA released a report, *Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products,* addressing the slowdown in innovative medical therapies submitted to the FDA for approval. They say that "the number of new drug and biologic applications and innovative medical device applications submitted to FDA has declined significantly. The report further asserts that developing products targeted for important public health needs (e.g., counterterrorism) is becoming increasingly challenging and that the current medical product development path is becoming inefficient and costly. Because of the rising product development costs over the last decade, innovators often concentrate their efforts on products with potentially high market return"[2] leaving behind such things as preventive vaccines against biological agents of terror which would provide a critical response to actual and potential acts of bio-terrorism. The FDA proposes that new tools are urgently needed to improve

predictability and efficiency along the critical path from proof of concept to commercial product.[2]

Many accomplished scientists in academia, government, and industry are collaborating to solve these challenges with development. Although there has been much recent success, "the fact remains that the pace of this development work has not kept up with the rapid advances in product discovery. The result is a technological disconnect between discovery and the product development process -- the steps involved in turning new laboratory discoveries into treatments that are safe and effective"[2] and useful to address certain public health needs such as counterterrorism.

This paper aims to investigate the use of the Axiomatic Design methodology as a tool in the biomedical industry to develop a product development *process* that addresses the challenges and needs of the Nation.

THE PROBLEM

The job of the CDER is to evaluate new drugs for safety and effectiveness before they can be sold. Their evaluation makes sure that the drugs they approve meet tough standards for safety, effectiveness and quality. The regulatory requirements to which companies must comply during product development are extensive and noncompliance is not an option. According to the Center for Drug Evaluation's report to the Nation in 2005, however, there is a recognized need to facilitate the product development of products such as countermeasures to protect Americans from biological, chemical, nuclear and radiological agents of terrorism.[3] In fact, an FDA report in 2004 described an urgent need to modernize the medical product development process—the Critical Path—to make product development more predictable and efficient. In addition to this public health need, biomedical companies today are being driven to become more operationally efficient due to the rapid pace of global competition and the increasingly strict regulatory environment.[4] Regulatory agencies are expecting more of medical device manufacturers in terms of process efficiency and *cross-functional* procedure and process definition driving organizations to improve their processes in order to expedite development in the interest of important public health concerns such as counterterrorism while still fulfilling their obligation to develop safe and effective products.

The regulations under which products are developed place great emphasis on the use of procedures to regulate and control how internal operations should be performed. According to the FDA, however, the current pharmaceutical regulations (21 CFR Parts 210, 211, 600 and 610) appear to provide some degree of flexibility for these processes as long as they comply with minimum criteria outlined in the regulations. [5] The FDA states that there is a need to modernize the scientific processes through which a potential human drug or therapeutic biologic is developed from "proof of concept" into a medical product.[3] The challenge is determining how to address this urgent need for speed against this regulatory environment.

Influence on the time it takes to maneuver through the product development process is due to both the process definition for the specific company under defined regulations and the product review of the product by the regulating agency. A drug company seeking to sell a drug in the United States must first design and test it. The clinical research is monitored by the regulating body to ensure that people who volunteer for studies are protected and that the quality and integrity of scientific data are maintained. The biomedical company then sends evidence from these studies to the regulating body to prove the drug is safe and effective for its intended use. The regulating body assembles a team of physicians, statisticians, chemists, pharmacologists and other scientists to review the company's data and proposed use for the drug. If the drug is effective and the regulating body is convinced its health benefits outweigh its risks, it is approved for sale.[3]

What has been an influence on the product development process definition in this industry today has been the very nature of the use of these types of products, preserving human life, and the stringent regulatory requirements that have historically dictated this process.

The problem is that the product development procedures that define product development operations have typically been so regulation driven, and all too often only a regurgitation of the regulation content, that they are missing the other more significant part in this effort - the requirements all of the stakeholders involved in that process. Commonly in the product development process, there is not a clear understanding of who all of the stakeholders might be, i.e. manufacturing, and what are all of those stakeholder needs. In the case of drug development along the critical path, there is also the need to recognize expanding external stakeholders. For example, the CDER has identified a stakeholder that may not be considered as part of the "normal" development process for certain medicines, the "vulnerable population". [3] The regulating agency has identified the need to foster the development of medical countermeasures for this vulnerable population. For example, a drug developed to block the uptake of radioactive iodine may be approved in tablet form yet this was not developed with young children in mind. But this medicine in a ready to use liquid form using an eyedropper to enable easy treatment for young children and newborns would better address this vulnerable population for this intended use.[3]

The cGMPs only constitutes the Agency's expectations. It does not take into consideration the specific needs of the company. So when processes are developed as a regurgitation of the regulations, companies may not have the most optimized process.

What is seen is that even if the procedures produce written compliance, what often happens is the internal "work-around" for those deliverables or tasks the stakeholders find non value-added. This now uncontrolled, unrepeatable process may lead to increased compliance risk resulting in interrupted production and distribution, product liability exposure and delayed product approvals. Likewise, this may also cause resource drains across the organization to complete audit corrective actions, repeat procedural tasks, re-test, re-work, and write revisions to the procedure. Ultimately, this leads to significant inefficiencies resulting in slower times to market, poorer product quality, and increased costs.

In the case of innovative therapies for important public health needs there is a great challenge to development under the processes used for "normal" drug development.

Therefore the need to redefine "normal" is upon us. Understanding this need, the government has overhauled the regulatory and quality control systems for pharmaceutical products and is encouraging manufacturers to modernize their methods, equipment and facilities.[5] Specifically for counterterrorism measures, the CDER has been taking an aggressive and proactive approach to their role in helping to prepare the nation for terrorist events, emerging health threats and emergency response to natural and man-made crises. They have put forth efforts to improve both their external polices, known as "current good manufacturing practices" or cGMPs as well as their internal programs for the review of an application's chemistry, manufacturing and controls sections. They are setting clear standards for the evidence needed to approve a drug, for safety and effectiveness testing, for drug quality and manufacturing processes that help medical researchers bring safe and effective new drugs to American consumers more rapidly. This strategic initiative is called *Pharmaceutical cGMPs for the 21st Century* [5]. They are also doing their part by working closely with manufacturers to see where streamlining can cut red tape without compromising drug quality. [3]

In light of the changing regulatory environment, companies have no excuse not to redefine their product development processes. Now the ball's in the court of the biomedical companies. As regulatory agencies are recognizing the need for engineered product solutions that can be trusted, the product development process by which these products are created must be reliable, optimized, and robust by being well thought through and meeting the requirements of *all* the stakeholders, both the forgotten internal and the expanding external stakeholders that define the system. Yet this optimized efficiency must still occur under the constraints of the government regulations and under the enforcement of the federal requirements for drug approval, manufacturing and labeling. So companies are faced with redesigning how they operate from a more systematic and comprehensive manner under the constraints and changing demands of the regulating agency.

The approach to redefining the product development process is where companies might get the greatest benefit and success in creating the best process to satisfy all stakeholder needs. Far too often, as companies have tried to redefine their product development process, the process definition becomes an exercise in subjective opinion; recalling previous experience from a different organization, and such other types of ephemeral "tools". So product development processes may still be designed without considering the requirements of all or of the expanding stakeholders. 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. Requirements can not be created in a vacuum and one size does not fit all, however. So each manufacturer has the responsibility to establish requirements for each type of product under development

A novel approach to quality system process design and development is to use and/or adapt the Axiomatic Design methodology to develop a framework for a product development process in the regulated biomedical industry.

WHAT IS AXIOMATIC DESIGN

Axiomatic Design 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." [6] 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.

The word DESIGN is used all over the world and in all industries. Its definition, however, 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."[6] Commonly, designers have designed "iteratively, empirically, and intuitively, based on years of experience, cleverness, and creativity and involving much trial and error."[6] 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." [6] 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."[6]

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.

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. [6]

Matrices 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}**

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

Uncoupled Design Matrix Decoupled Design Matrix

2. **process design matrix, B,** which shows the relationships between DPs and PVs where the {PV} is the PV vector in the process domain - **{DP} = [B] {PV}**

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.)[6]

Design Axioms: Governing this analysis and decision making process for the best design 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: independence and information. The independence axiom states that "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."[6] 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.[6]

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 effect the other so this design is uncoupled.[6]

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."[6] 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.

AXIOMATIC DESIGN IN THE BIOMEDICAL INDUSTRY

Design means many things to many people and is an interplay between what we want to achieve and how we want to achieve it [6]. Quality professionals in the biomedical industry think of design in terms of quality system processes like the product development process. In the AD methodology and research, the term "process" typically refers to a *manufacturing* process. There is little evidence the AD methodology has been applied to designing a robust and optimized quality system process in a biomedical industry. Some say, however, that companies should consider treating the product development process with the same level of rigor that is used for the products it creates. Using recognized methodologies to develop the product development process can ensure both regulatory compliance and business excellence. [7] Therefore Axiomatic Design may be a good option to use to design a quality system product development process to address the issues with time to market while developing a safe and effective product.

In order to prepare for events that affect the public health critical infrastructure, AD may be used and/or adapted to develop a framework for a product development process in the regulated biomedical industry. Proving this may ultimately show biomedical companies how to operate more cost-effectively, efficiently, and successfully, as it relates to all stakeholders, by creating the right process for the right company.

In one example AD was applied to develop part of the product development process in the biomedical device industry related to the Code of Federal Regulations part 820.30i, Design Changes. The regulations states "Each manufacturer shall establish and maintain procedures for the identification, documentation, validation or where appropriate verification, review, and approval of design changes before their implementation." [8]

The conclusions of this work stated that using axiomatic design "allows the procedure designer to easily identify user needs and convert them into functional requirements and design parameters. Once this is done, it is possible to validate the system after the design parameters have been linked to the product structure. Once the validations are complete, the company will have a new set of procedures – developed with functional needs in mind – that meet the needs of all the users."[7] Likewise, the supporting process documentation will provide adequate evidence to address any regulatory enforcement efforts.

FUTURE RESEARCH

Our research efforts are directed towards applying axiomatic design in the biomedical industry. Our work in this area is focused on expanding the AD methodology to cover the product development lifecycle process as it applies to biomedical drug and device organizations. This research is evolving such that there are opportunities to 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. The product development process in the regulated medical device industry, however, is unique from other development processes in that it should include a regulatory submission/clinical investigation domain from which to zigzag back and forth. This is different than the compliance regulatory requirements that would be used as constraints in the functional domain. Therefore, there is a need to adapt and expand the AD methodology to add this domain for this type of industry. Likewise, there will be the need to expand the rules of AD as it applies to developing an uncoupled design in a cross functional process.

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