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Concept of Six Sigma in the Pharmaceutical Industry

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ABSTRACT

Six Sigma is a process that analyzes the flaws and faults in a company. It helps the company in producing quality products at a lower cost that will satisfy the client. This idea mostly uses two approaches: DMAIC [Define, Measure, Analyze, Improve, Control], which corrects the flaws in current processes, and DMADV [Define, Measure, Analyze, Design, Verify], which starts a new process when the old one entirely fails to accomplish its goals and objectives. The tools and techniques used in this article include flow charts, checklists, Pareto diagrams, causes, and effects, statistical process control, etc. Six Sigma tools and procedures are assessed to determine whether they are being implemented in the right way that helps the customers. The client benefits, such as improved financial assistance for new development projects, lower prices, quick market deliveries, and increased product quality, are measured using the key performance indicators. As a result of these characteristic features, numerous organizations have adopted Six Sigma. Nevertheless, only a small number of pharmaceutical companies are members of the ISSSP [International Society for Six Sigma Professionals], Eli Lilly, Johnson & Johnson, and Novartis. Six Sigma deployment is entirely dependent on management and the supporting infrastructure, but it is equally applicable to research and development. It rectifies the flaws, sets the objectives, and specifies how to integrate R&D into corporate objectives. Organizations that have adopted the Six Sigma idea in their quest for perfection in their business have seen an increase in profit of 20%, 40% growth in market shares per year, and a 10% decrease in the cost of production for sales. From an average of 35000 faults per million operations to an almost non-existent 3.4 defects per million activities, there has been a drop in defects.

KEYWORDS: Six Sigma, Minimizing Defects, DMAIC, Process improvement

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1. INTRODUCTION

By eliminating variance, minimizing defects and errors, and improving quality and efficiency, Six Sigma is a set of approaches and technologies used to enhance business processes**.** Some of the most successful forms in the world have embraced Six Sigma, resulting in savings of billions of dollars, dramatic gains in the speed and capacity of their processes, and the development of new, stronger customer relationships. A flexible approach called Six Sigma is utilized to achieve, maintain, and maximize company success. With the rising adoption of Six Sigma, there is a wealth of published data. GE, Siemens, Nokia, and Toyota are a few examples of businesses that have adopted Six Sigma [1]. Six Sigma is a collection of numerical instruments used in quality management to create a framework for process improvement. The expression alludes to a statistical evaluation of the degree to which a process deviates from perfection [2]. Currently, in health care, Six Sigma is thought to be one of the top-quality improvement methodologies.

1.1 History

The six-step method was first offered by Motorola University.[3] Motorola developed the Six Sigma methodology in the 1980s in reaction to market share losses that made the business recognize that quality needed to improve if it wanted to compete with, in particular, the quickly expanding Japanese manufacturing industry. The Design for Manufacturing training program, from Six Sigma's inception in 1988, has been developed into a supplement to Total Quality Management (TQM). The Six a project-driven management strategy called the "Sigma method" aims to continuously minimize flaws in an organization's goods, services, and operations. It serves as a

commercial tactic that emphasizes locating and removing factors that contribute to process errors or failures by concentrating on those that are crucial to the customer. Bill Smith, a Motorola engineer, devoted a lot of time to persuading Motorola's upper executives that his new quality control system, Six Sigma, would have a big impact on the business.

To continue improvement for selected or desired targets in Six Sigma or within the confined limits, a 5step process called DMAIC is utilized i.e.., Define, Measure, Analyse, Control, and Improve. It is used to find a solution that can improve process quality and is also a suitable choice for cost-effectiveness, difficulties, and disadvantages.

Due to generic competitors' rivalry and production mistakes, the pharmaceutical business is experiencing declining sales. By reducing the minimum amount of waste and errors, numerous companies have started increasing the efficiency of manufacturing along with the working processes. [5]

Six Sigma can be introduced into the pharma industry through the following possibilities:

- Six Sigma can be executed in the pharmaceutical industry to modify conventional ways to perform clinical trials and start to take charge of the use of the Six Sigma concept.
- By launching new businesses that cannot be supported by in-house process improvements.

1.2 Reasons for Six Sigma:

By employing data and statistical analysis to eliminate undesirable variations in crucial process parameters, Six Sigma aims to increase customer satisfaction and lower costs.

- Critical parameters are those that have an impact on features that matter to the client or end user. However, it is crucial to understand that the Six Sigma method is not a statistical system. The ultimate objective of Six Sigma is to change the entire mind-set and culture of the organization to create systems and processes that are as close to perfect as is humanly possible, ensuring that they are operating at the highest levels of performance. It uses statistics as tools for the use and interpretation of data.[6]
- The delivery of approved units increases as a result of reducing process variation, which also lowers costs. Additionally, this reliable procedure prevents the timely and expensive investigations brought on by process aberrations. To confirm that the implemented changes have had the desired impact, the Six Sigma activities employed to minimize variation should be immediately measurable in terms of costs and customer satisfaction. [7]
- According to the Six Sigma system, a process is considered to be in equilibrium when the distance between its mean value and its nearest tolerance limit is at least six times that process's standard deviation; this equates to a maximum of 3.4 faults per million units.[8]Although this level is practically unachievable, it serves as the aim of Six Sigma; the objective of Six Sigma is to continue working towards it by using methodology to continually find areas that may be improved.

2.0 SIX SIGMA METHODOLOGY:

DMAIC

- According to Motorola CEO Robert Galvin, in order to properly install and employ Six Sigma, the company's top management must be involved and completely support this approach. The Six Sigma methodology concentrates on a smaller number of projects that guarantee high profitability and runs the projects over a very brief period of time to ensure that individuals maintain their focus and enthusiasm on the project. [9]
- The theory and execution of Six Sigma approaches make up the majority of the Six Sigmaliterature.
- In Six Sigma, there are two main techniques for improvement. The first methodology, DMAIC, may be broken down into five phases: define, measure, analyze, improve, and control. It is used to improve already-existing processes. [10]

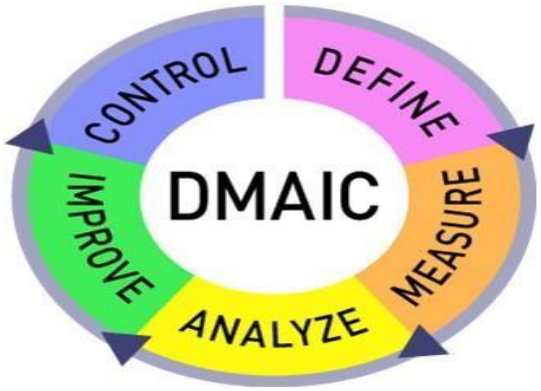

Fig: 1: DMAIC

- The DMAIC approach, which focuses on enhancing current processes, and Design for Six Sigma (DFSS), which focuses on creating new products and processes, are the two fundamental approaches in the Six Sigma methodology, as shown in Fig 1.
- It is a systematic five-phase methodology utilized to be able to meet the defined targets inSix Sigma in present processes or within set boundaries. The duties and activities in eachof the five phases are carried out using various methodologies and technologies. This methodical approach fosters motivation and a laser-like concentration on maintaining the implemented changes, in addition to offering a clear work framework.
- Define: The issue is recognized and explained in detail. The project team has been chosen,and the aim has been established. [11]
- Measure: To establish a baseline for the present performance, the symptoms of the issues are determined, and objective data is gathered. The main objective is to determine the sources that are deemed to be primarily responsible for the problem. The symptoms in Six Sigma

are defined as the output of the process that is producing the problem.

- Analyze: In this stage, theories on the root causes of the issues are developed, and put to the test, and the hypothesis is either accepted or rejected. The result of this stage is the problem's underlying cause. [12]
- Improve: This phase begins with a comparison of the available options to ascertain which approach would most successfully get rid of or lessen the source of the issue. Once an improvement approach has been chosen, the process for putting it into practice is created to make sure the improvement reaches the project's objective and that the natural resistanceto change is overcome to make sure the implementation goes as planned. Before the modification is fully put into place, the process's efficacy is checked.
- Control: To verify that the actual outcomes of the changes meet the anticipated results and thatno recurrence is found, this final phase is integrated into the normal organization. The optimized process is monitored by appropriate quality controls. [13]
- The second methodology, Design for Six Sigma (DFSS), is used for new processes or when the current procedures fall short of achieving company goals, like client pleasure. DFSS methodology can also be divided into five phases (DMADV): define measure, analyze, design, and verify. Further studies state that DFSS is a powerful approach to designing products, and processes in a cost-effective and simple manner. Applications of DFSS have also varied, from high-tech manufacturing to designing new housing.

DMADV

a. The **DMADV** approach is very important to problem-solving within any enterprise using Six Sigma in their product and service development processes.

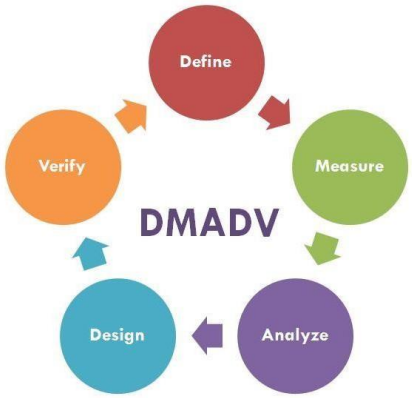

Fig: 2: DMADV

b. Define: describing the DMADV methodology's first phase, which identifies the project goals and client deliverables. This step's objective is to clearly define the project's aim, project scope, available resources, and high-level schedule. During this phase, the project must be defined clearly, and each strategy and aim must be in line with the demands of the organization and its clients, as shown in Fig 2.

c. Measure: Its goal is to thoroughly comprehend the customer's needs and create the crucial quality (CTQ) that will satisfy them. To do this, divide the market into various segments, and then create CTQs for each segment. Metrics and measurement systems must be developed for each CTQ that has been identified. Following that, these technologies will assist in capturing the performance of the Critical Quality Attributes (CTQ).

d. Analysis: The third stage of the DMADV process is analysis. The best design ideas that will address customer demand (CTQ) are developed during this phase. The analysis phase's goals are to develop alternate design concepts for each CTQ, assess the alternative design concepts, and then integrate the most effective aspects of the design concepts to create the final design.

e. Design: The fourth phase in the DMADV approach is design. The best design idea that emerged during the analysis phase needs to be turned into a prototype during this stage. A prototype of the design model that will be examined in the Verification phase is what the design phase is for.

f. Verify: The fifth and last phase of the DMADV process is verified. This phase involves testing the prototype of the best design to ensure that it performs as expected. This is done to ensure that the design satisfies the customer's expectations, such as protecting the goods from harm during distribution and preventing packing damage. The Verify phase's objectives are to test the detailed design prototype, examine the test samples, determine whether or not to scale up the design and finish the DMADV project.

g. The DMADV framework aims to achieve the ideal balance between three views, namely the demands of the customer, the process or procedure to meet those needs, and the company's goal or objectives. It is an all-encompassing approach at the strategic level that seeks to assist in resolving issues pertaining to the creation of a new good or service as well as its application and management. The DMADV model has shown extensive success over the past three decades in a variety of industries, including manufacturing, services, transportation, pharmaceuticals, etc.

2.1 A Few Examples of the usage of DMADV are mentioned below:

a. To create a new package for a product or to make an existing package better.

b. High-quality product design is important in the healthcare industry since errors in medical equipment can be fatal.

c. To reduce flaws in all production processes, from production to transactional and from productto service providers in several fields. For instance, a service

provider wishing to launch a new customer support team may utilize DMADV to determine the number of employees needed foreach shift or the turnaround time for customer service responses.

d. However, the DMADV method's execution prioritizes efficiency and standardization over originality and creativity, which is one of its key drawbacks. Although DMADV development appears linear, because of the complexity of most projects, it must actually be iterative. To deliver better projects, DMADV must be flexible and nimble.

e. The use of build-in by design is therefore studied in the interviews in this thesis, as it is considered vital to completely obtaining consumer advantages in the pharmaceutical sector.

f. Another crucial element that sets Six Sigma apart from the majority of other outstanding programs is its instructional framework. It is crucial that users have a thorough knowledge of the tools and recommended practices in order to use them effectively. As a result, Six Sigma employs a planned educational program involving Six Sigma leaders and experts on various levels. [14] These levels get their names from Japanese martial arts, where the titles "black belt" and "green belts" are depicted.

g. Additionally, Six Sigma develops specialized jobs within the organization rather than adding more work to already overworked managers or workers. [15] The relevance of employee training is considered to be extremely important and is thought to have a significant impact on the success of Six Sigma implementation. As a result, the importance of training is examined in the interviews conducted for this thesis.

2.2 Maximizing Six Sigma's potential for your organization*:*

i. The work in all areas of the organization must use the Six Sigma mindset in order to maximizethe benefits of the methodology. [16] Since nonmanufacturing operations are only about 70% efficient, data shows that there are significant gains to be gained by adding them.

ii. General Electric saw that the potential of Six Sigma was much bigger than the present applications in their production processes as they continued to expand the Six Sigma system first developed at Motorola. [17] It explains how Six Sigma may be used to improve numeroustypes of processes, including financial, administrative, and new product development, and howchanges are implemented. In addition to offering a clear framework, its use greatly lowers functional barriers. By doing this, it is made sure that the system's bottlenecks or variations' underlying causes are actually removed and not just ignored. The potential gains from Six Sigma implementation are equally important, if not more so, in the service and non-manufacturing sectors. This further reinforces the advantages of implementing Six Sigma throughout the entire organization.

iii. Additionally, it's critical that the Six Sigma implementation be tailored to the requirements ofthe particular organization. "There are many Six Sigma Ways" and sticking to a predetermined plan will guarantee poor implementation. [19] There are no explicit Six Sigma standards or certifying organizations that direct the implementation, unlike, for instance, an ISO-9000 implementation. No matter how similar the processes or organizations appearto be, it is difficult to "copy and paste" a Six Sigma implementation from another company. Instead, the expertise of the organization must be utilized. From a Six Sigma perspective, the organization's application of knowledge is also crucial.

3.0 Tools and Techniques of Six Sigma:

There are numerous tools and methods that can be used in Six Sigma projects that are both in the literature and in the public domain. [41] Although the majority of these tools are already well-known and used in other settings, Six Sigma offers a customer-focused, well-defined methodology backed by a clear set of all-inclusive tools for process improvement.[20] Flowcharts, checklists, Pareto diagrams, cause-and-effect diagrams, scatter diagrams, histograms, and statistical process control are some of the fundamental DMAIC tools that are frequently utilized at the Yellow-Belt level of competency. [21] The Black-Belt level often includes more sophisticated tools like regression analysis (for example, within-indicator variables, curvilinear regression, and logistic regression), hypothesistesting, control charts, and the design of experiments. This also implies that Six Sigma may be seen as a collection of tools and procedures that were already in use long before Motorola created this methodology.[22] A robust of essential improvement tools to be used within the DMAIC process isrequired because tools are also available in a variety of formats, such as models, analysis templates, and procedures. As a result of this abundance of techniques, the process becomes more complicated. Any Six Sigma project should take into account the fact that tools will need to evolve as the project progresses. In the early stages of a complex manufacturing system, simple instruments are frequently sufficient to eliminate defects. Although there are many different tools and techniques, it is crucial to use the correct tool in the right situation in order to get the desired outcome. This may explain why it is usual practicein the literature to list the primary tools for each of the five DMAIC methodology phases. However, there are no established methods for selecting the best instruments for a given situation. [23] Companies have incorporated a variety of tools into the Six Sigma approach throughout time to increase efficiency and close any gaps that may have existed after adoption. These toolkits comprise statistical and analytical methods from the domains of operations research and industrial engineering. In this case, these tools strengthen the theoretical underpinning ofthe practical and industrial approach to achieve improved

equipment and resource use. [24]

3.0 CUSTOMER BENEFITS FROM SIX SIGMA

The primary goal of this thesis is to examine how Six Sigma implementation improves the pharmaceutical industry's customers. Key performance indicators can be used to track the outcomes of implementing adjustments and improvements. The significance of selecting pertinent metrics

- Improved product quality
- Increased financial support for new development initiatives
- Lower prices
- Quicker market deliveries

to monitor how each Six Sigma project affects customer satisfaction. [25]

In this thesis, customer benefits are quantified using the KPIs listed below:

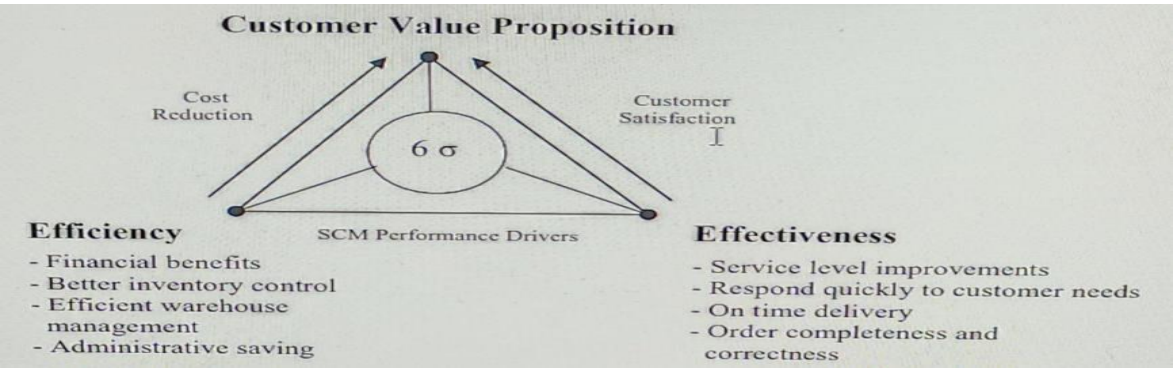

Fig: 3: customer benefits

As mentioned in the introduction, a number of pharmaceutical companies are under increased operational and financial stress as a result of a number of factors, including eroding patent protection, a lack of pipeline drugs, and consumer demand for more innovative products at lower prices. As a result, many of the key operations and procedures in the pharmaceutical industry must be altered in order to better reflect the shifting business environment. Additionally, according to a survey conducted by Lenzer in 2004, only 13% of Americans think that pharmaceutical businesses are "generally honest and trustworthy". Additionally, accordingto this survey, the public's trust in the pharmaceutical industry has declined more quickly thanthat of any other, as shown in Fig 3.

Since the customer definition is broader in the pharmaceutical industry than it is in many others, as was also stated above, using Six Sigma in this sector necessitates extra caution when identifying the customer.

The pharmaceutical sector is therefore heavily regulated to ensure that businesses comply with all regulatory agency standards, yet many basic procedures do not fully fill the needs of the market and customers today. [26] In particular, it uses the process of drug development as a shining example. In fact, the time it takes to create a medication now is longer than it was ten years ago. The application of Six Sigma is one possible response to the business problem and challenge of high costs and lengthy lead times for product development. [27]

Companies use Six Sigma for a variety of reasons, particularly in the R&D department. Some of the key goals are to save costs, shorten time to market, and improve the process and productquality.

4.0 SIX SIGMA- IMPLEMENTATION AND USE

Only a few pharmaceutical businesses are mentioned among the more than 300 organizations that make up the International Society for Six Sigma Professionals (ISSSP) membership, according to. [28]

This shows that there is still much that Six Sigma and other industries can teach the pharmaceutical industry. However, many pharmaceutical firms have adopted Six Sigma and are using it effectively to carry out their company goals. Baxter, Eli Lilly, Johnson & Johnson, and Novartis are a few pharmaceutical businesses that have used Six Sigma. [29]

No matter what industry or market the company is operating in, committed leaders, management, and supporting infrastructure are critical components for the effective implementation and utilization of Six Sigma. In order to learn from other industries and utilize the available knowledge and experience to the fullest, it is crucial to see the similarities rather than just focusing on the differences in the problems that businesses face and the factors that make a successful implementation possible. [30] The effectiveness of Six Sigma is thought to be greatly influenced by dedication, effective leadership, and benchmarking, all of which are considered to be of the utmost importance.

Six Sigma was initially mostly utilized in manufacturing processes, where its advantages alsoapply to R&D processes. The unique nature of the work done in the R&D departments, however, raises a lot of questions about whether Six Sigma should be used in this kind of work. There isn't much agreement in the literature regarding whether Six Sigma encourages the originality and creativity required in R&D work to be able to produce new products or not. [31] Teamwork and intellectual freedom are necessary for fruitful medical research; hierarchical reporting systems and committee decision-making are two characteristics that stifle.

In order to ascertain whether Six Sigma designs will satisfy the requirements of the specific R&D working environment in question, it is crucial to analyze the organizational management structure and procedure. As was previously mentioned, this is an essential phase to guarantee that the offered improvements genuinely help the organization.

The difficulty in product creation is controlling how much variation there is within a process while maintaining innovation.[32] Furthermore, applying Six Sigma techniques to the operations that are repeated inside R&D organizations will free up more time for experimentation and invention, which will ultimatelylead to an increase in creativity. [1,10] After further investigations, it was proven that Six Sigma and its tools would guarantee that R&D results in superior products that boost profitability. [33]

It also describes the advantages of implementing Six Sigma tools in the R&D pharmaceutical department of GlaxoSmithKline (GSK), which led to improved knowledge exchange due to increased teamwork and standard best practice procedures. Productivity was increased by eliminating and decreasing time spent on repetitive tasks, thereby reducing cycle times. It provides additional examples of successful Six Sigma implementation in R&D departments tosupport these findings. He uses case studies of businesses to demonstrate how Six Sigma has improved productivity and overall product quality while also increasing sales of new products.[34]

In R&D, "eliminating faults" is challenging because work defects require systematic improvement. Numerous firms have demonstrated how Six Sigma principles are taught to technical personnel, how to include R&D in corporate goals, and how to avoid spending a fortune on relatively infrequently used instruments in the workshops of the Industrial Research Institute's Six Sigma in R&D Project.

Being the greatest at everything you do can have a near-miraculous influence on yourorganization and the bottom line, according to the deceptively simple premise behind Six Sigma. Its purported benefits actually seem almost too good to be true. However, those who have fully embraced them assert that they are not exaggerated.

The stated advantages of pursuing Six Sigma perfection include a 20% boost in profit marginswithin a year, a 4% annual increase in market share, a drop in production costs to less than 10%of sales, and a 10,000-fold quality improvement from an average of 35,000 defects per millionoperations to an almost non-existent 3.4 defects per million activities.

Of all industries, the pharmaceutical sector has the most regulations. Regulatory affairs expertsplay an important role in the development of new products and serve as a liaison between the industry and regulatory bodies like the FDA. The principles of variation management and reduction are provided by Six Sigma as a problem-solving methodology in a number of sectorsto aid in the conversion of old processes into fresh, effective approaches.

4.1 Case Study: Optimizing Data Entry Process

It takes 14 years on average to find a new medicine and develop it. Six Basic research, discovery, preclinical development, clinical development, and Food and Drug Administration (FDA) approval are the five stages of the process. When a new drug substance is tested on human subjects, several clinical trials are conducted as part of the clinical development phase.

The cost of bringing a new medicine to market is 68% of the total cost during the clinical development stage. Clinical development phases II and III cost 53% of the total and take 4.5 years, or 32% of the overall time, to obtain test findings that are suitable for a New DrugApplication (NDA) filing. The formal FDA application for a government-approved authorization to market a novel medication in the United States is known as an NDA. [37]

Table: 1

	Basic research	Discovery	Pre clinical development	Clinical development			FDA filing/approval and launch preparation
				Phase 1	Phase 2	Phase 3	
Milestone		Disc Target overy	Lead Candidate	IND filed		NDA filed	NDA approval
Duration (years)	2.5	3	1	1.5	2	2.5	1.5
% Years by phase	18	21	7	11	14	18	11
% Years by function	Research: 46%			Development: 43%			Other: 11%
% Cost by phase	4	15	10	15	22	31	3
% Cost by function	Research: 29%			Development:68%			Other:3%

Reproduced with permission from Liu.[6]

The average number of studies per NDA has climbed from 30 to more than 70 during the past20 years, and the average number of patients in a submission increased from 1576 to more than4200 between 1980 and 2000 [38].

Although the FDA bases its decision to approve a new medicine for sale largely on the findingsof clinical research,

the organization will not permit the administration of a wholly unidentifiedand uncharacterized molecule to human subjects. The FDA demands data on the drug's administration to lab animals before clinical work can start. The FDA evaluates the drug's safety for initial administration to people using the information from these studies. A pharmaceutical company will put together and submit an NDA to the FDA for in-depth assessment and scrutiny when it is satisfied that it has enough evidence to show that a new drug issufficiently safe for the market. A pharmaceutical company can start marketing its products inaccordance with the Code of Federal Regulation.

The needs of the pharmaceutical industry cannot trump ethical obligations to clinical trial participants or the goals of science. There should never be any consideration for mitigating factors or compromising patient well-being in order to speed up clinical trials. Clinical and scientific researchers must develop and test new medications, and their setbacks are not just motivated by altruism. An organization's social and ethical obligations go beyond following the law and the legal system. They discuss matters of obligation and the foundational values that support this duty.

The FDA's investigational new drug review process (FDA, 1997) outlines the step-by-step procedures that a pharmaceutical company must follow to receive FDA approval for an exemption from the law that forbids the shipment of unapproved medications in interstate commerce. The application includes a compilation of every piece of information that is currently available regarding the substance, a description of the clinical research strategy, and the exact protocol for the Phase I study (i.e., the testing of the new medication on healthy human volunteers). Pharmaceutical companies typically use special three-part Case Record Forms (CRFs) for clinical trials to allow doctors at investigator sites to record protocol-specified clinical data about patient vital signs and medical indicators of the efficacy of the drug throughout the multi-year trial. Tens of thousands of CRFs must be collected from hundreds of clinical trial sites for every large clinical study, and their reliability is directly correlated with the reliability of the devices used to gather the data.

The most important step in the clinical trial process involves source data, which is the original records of any clinical observations, discoveries, or other trial-related activities required for the trial's reconstruction. Their dependability directly relates to the dependability of the data collection tools. Electronic data capture (EDC), also known as original clinical findings, observations, and other medical indications, is becoming more and more common. By removing transcription errors, streamlines the clinical trial procedure and ultimately cuts the study's time.

This case study investigates the CRF data input procedure in a typical Phase III trial, taking into account the significance of the time and expenses of clinical development. The goal of this case study is to find a ground-breaking way to cut cycle time and error rates when inputting CRF pages into a data management database in a conventional clinical trial by more than 70%.The process for optical scanning and the current CRF handling procedures have both been revised. [39,40]

5.0 CONCLUSION

Six Sigma is a statistical tool for supplying and improving the caliber of products and services. The objective is to raise the Critical to Quality (CTQ) performance metrics at the Six Sigma level, which represents customer expectations, using a suite of data analytic tools. Six Sigma is a systematic approach to data collection and statistical analysis. It was created with the intention of finding and fixing defects while maintaining the product's quality. This technology is useful when it comes to improperly framed procedures. Six Sigma has become a cornerstone of the world's top organizations because of its proven track record of generating solid financial outcomes. Errors decreased when the Six Sigma technique was applied.

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