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QUALITY BY DESIGN (QbD) on CLINICAL TRIALS ACTIVITIES – A REVIEW

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Abstract:
Pharmaceutical industry is constantly looking for ways to ensure and enhance product safety, quality and efficacy. However, drug recalls, manufacturing failure costs, scale up issues and regulatory burden in recent past suggest otherwise. In traditional quality by testing (QbT) approach, the product quality and performance are predominantly ensured by end product testing with limited understanding of the process and critical process parameters. Regulatory bodies are therefore focusing on implementing quality by design (QbD), a science-based approach that improves process understanding by reducing process variation and enabling process-control strategies. In this regards, pharmaceutical industry is currently undergoing a significant transformation to stream line their R&D process, provide greater manufacturing flexibility and control, and to reduce regulatory burden. However, there is a limited understanding and major concerns regarding the implementation of QbD principle in the pharmaceutical arena. The objective of this review article is therefore to provide a comprehensive understanding on various aspects of QbD, along with addressing the concerns related to its implementation.

KEYWORDS: Quality by Design, Design of experiment, Quality risk management, Design space, Quality target product profile.

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1 INTRODUCTION:

The pharmaceutical market has been considered as one of the highly regulated sectors, which has been continuously providing quality drug products for human use to provide desired pharmacotherapeutic effects for the treatment of diverse ailments. From the past few decades, however, the pharmaceutical industry has been continuously facing challenges in delivering quality drug products. As per the news article published in The Wall Street Journal on September 2002, it was reported that "although pharmaceutical industry has a little secret as it invents futuristic new drugs, yet its manufacturing standards are lag far behind the potato chips and laundry soap makers." The major issues pertaining to the poor quality of drug products could be attributed to more than one reasons such as variable starting materials, lack of manufacturing process automation and control, and improper understanding on the product and process parameters. Fig. 1 shows the key sources of variability associated with the development of pharmaceutical products, which are responsible for product recall in a major manner.

Due to the poor pharmaceutical product quality, the first initiative was a step forward by the United States Food and Drug Administration (USFDA) for inculcation of quality paradigms into pharmaceutical development and regulatory practice. In this regard, a concept paper was published in 2004, which highlighted the vision of agency for revolutionizing the quality paradigm in the form of "Pharmaceutical cGMP for 21st Century". After this initiative, the International Conference on Harmonization (ICH) instituted various regulatory guidance (Q8, Q9, and Q10) and set forth the concept of quality by design (QbD) as a holistic approach, which delivers high-quality robust drug products.

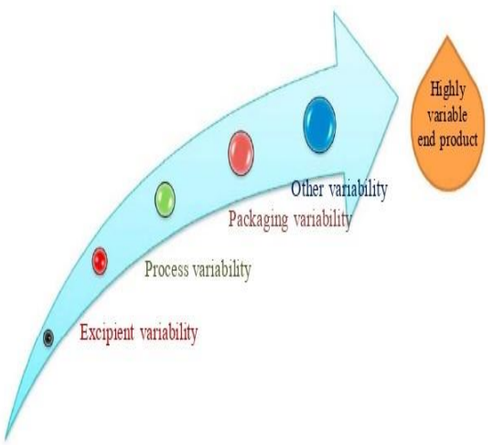

Fig. 1 Sources of variability in drug product quality.

EVOLUTION OF QbD CONCEPT

QbD is not a new concept for the world. The concept was formulated by J.M. Juran, an American Engineer, in the early 1970s through his famous book "Juran on Quality by Design", which was later adopted by several technology-driven areas like, telecommunication, automobile, and aviation industries engaged in the development of high-quality products and services. The concept was later adopted by health-care industries, and especially utilize by medical device manufacturers in the 1990s. QbD into the pharmaceutical industry entered quite late in 2004, when USFDA took initiative for improving the standards of pharmaceutical manufacturing.

Fig. 2 Quality system indicating various cross-functional systems involved during pharmaceutical product development. (Adapted from USFDA Guidance for Industry Quality Systems Approach to Pharmaceutical CGMP Regulations.)

More- over, this system also endeavoured to facilitate scientific innovation and continuous improvement throughout the product life cycle. Fig. 2 illustrates in detail pharmaceutical quality systems, which contain multiple systems marked with control on the production process, facilities and equipment maintenance, laboratory control monitoring, material management, packaging, and labeling control.

ICH instituted three different guidelines for implementation of the culture of quality into pharmaceutical development practice. These include ICH Q8, Q9, and Q10 guidelines, which act in tandem with each other to potentiate quality development. ICH Q8 primarily aims for Pharmaceutical Development to design a quality product and its manufacturing process to consistently deliver the intended product performance. ICH Q9 primarily aims for Quality Risk Management principles, which as a part of effective quality system, help in identifying the probability of occurrence and severity of risk. ICH Q10 describes the Pharmaceutical Quality System, which is based on the International Standards Organization (ISO) principle related to Good Manufacturing Practice (GMP) regulations, and also complements ICH Q8 and Q9 guidelines for holistic improvement in the quality

PHILOSOPHY AND PRINCIPLES OF QbD

Based on the heels of Juran's philosophy and culture of quality, pharmaceutical QbD also relies on development of drug product(s) and process(es) using systematic approaches and rational scientific principles for achieving target quality in the end product. With QbD around, the predefined objectives of the target quality enable zero quality defects and avoid quality crisis. Many scientists consider quality as a matter of conscious intent and meaningful execution of the operations involved in the manufacturing of the drug products. QbD also facilitates improvement in quality by thoughtful planning and meaningful execution. Hence, QbD is also called quality by planning, but not by chance.

Use of sound scientific principles and quality risk management (QRM) are the two key enablers of QbD philosophy, which provides enhanced products and process understanding on the target drug products.

STAKEHOLDERS OF QbD

There are three major stakeholders of QbD, which include the end- consumer (patient), pharmaceutical industry, and regulatory agency. Among these, the end-consumer takes the top most position of the QbD triangle (Fig. 3), where patient health is the ultimate objective of implementing QbD principles into product development practice.

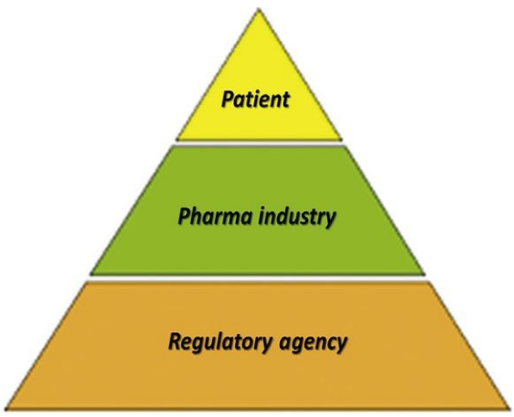

Fig. 3 QbD triangle integrating three major key stakeholders.

KEY ELEMENTS AND STEPS FOR EXECUTION OF QbD

Step I: Ascertaining Drug Product Objective(s)
Step II: Identifying the Critical Quality Drivers
Step III: Prioritizing the Input Variables
Step IV: Quality Risk Management (QRM) Approach
Step V: Factor Screening Study
Step VI: Factor optimization study
Step VII: Identification of Design Space and Optimum Formulation Design space.
Step VIII: Validation, Scale-up, and Production
Step IX: Control Strategy and Continuous Improvement

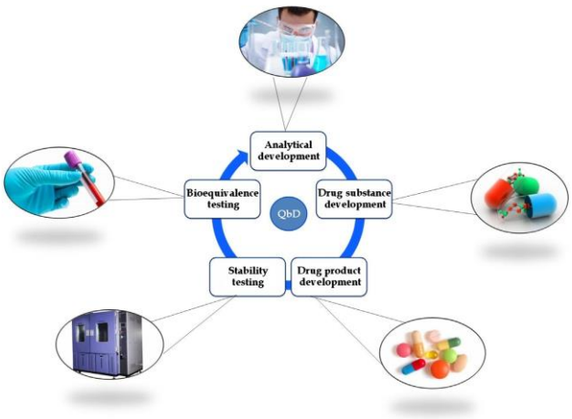

Fig. 4 Omnipresence of QbD at various stages of product development.

2 AIM

The main aim of QBD is to achieve meaningful product quality specifications that are based on clinical performance. T0 increase process capability and reduce product variability and defects by enhancing product and process design,understanding,and control [1]

Everybody is in favor of high-quality clinical trials. But what does that mean The clinical trials enterprise has long assumed that when it comes to ensuring trial quality, data is king and more is better. Not only was it Cleaned, and validated. In fact, this kitchen sink concept, commonly known as “100 percent source data verification,” became so Ingrained that it was considered risky not to collect ever-increasing volumes of data and metadata. However, growing evidence suggests That a myopic focus on the accuracy of each data point, regardless of its criticality, adds little — if anything — to trial quality and safety, While incurring significant expense and effort[2]. This has prompted interest in more tailored approaches that are informed both by trial Design and how trial conduct influences quality. Such approaches can help ease unnecessary burdens for trial participation and conduct And, therefore, improve the efficiency of drug development and ultimately bring new products to patients more quickly.

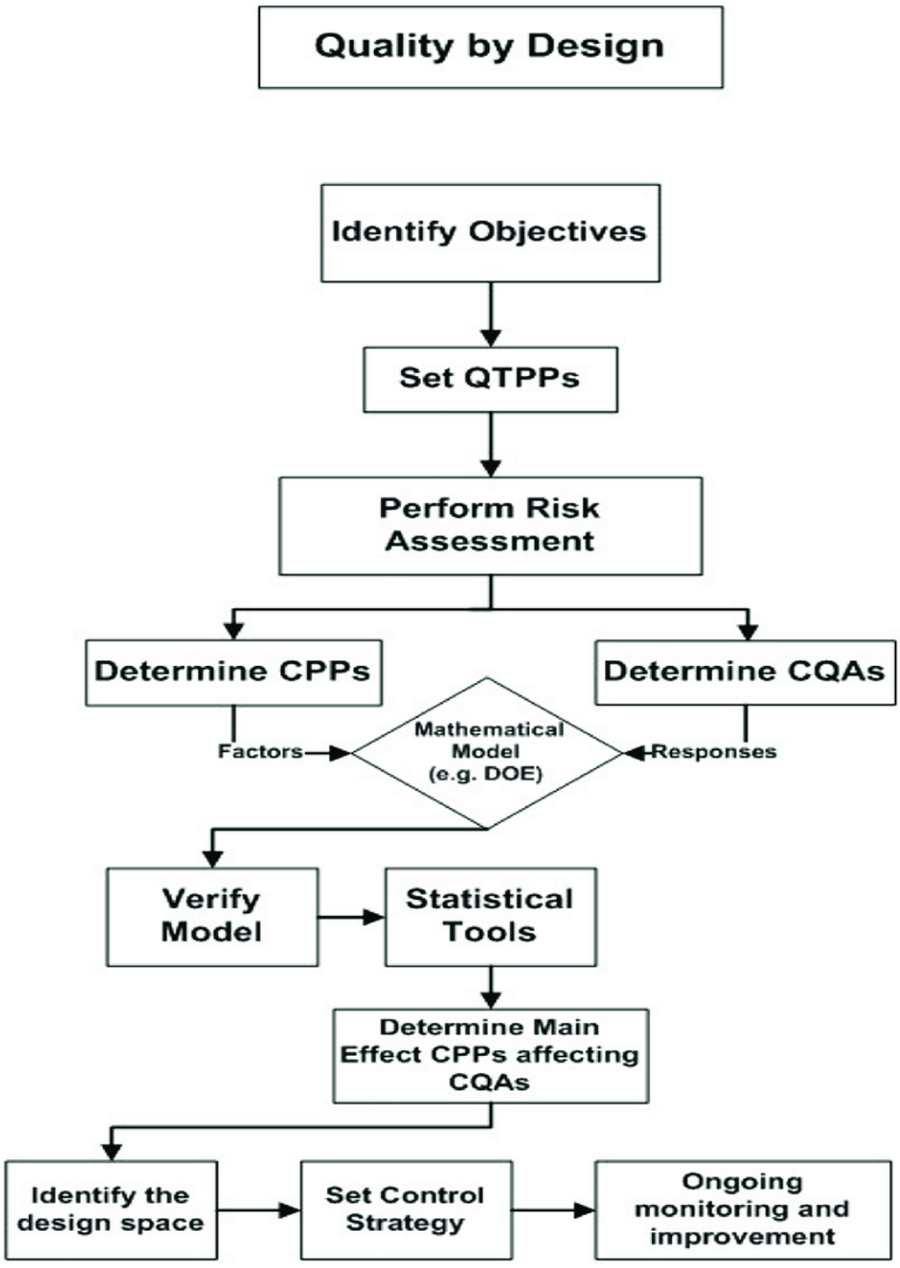

Fig 5: Approach To Quality Assurance And Risk Management

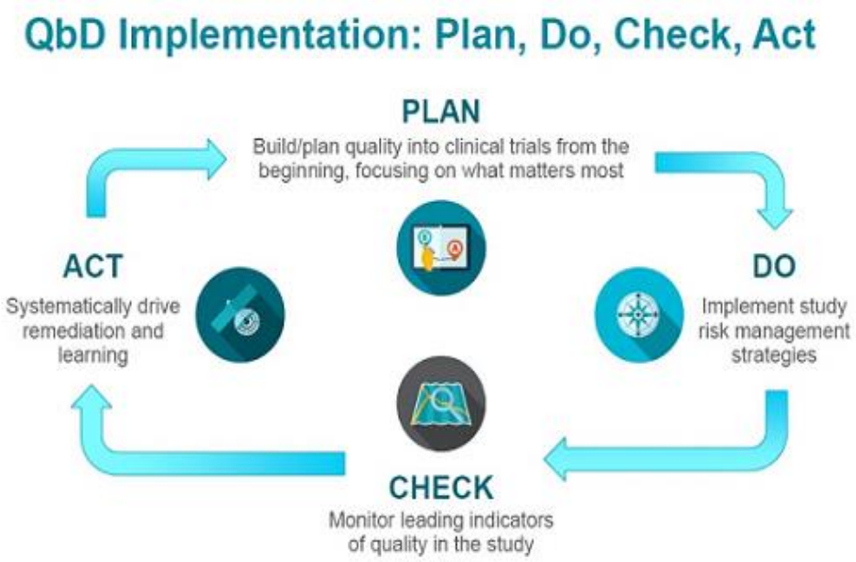

Fig 6 : QBD Implementation

Too Much of A Good Thing

- Clinical trial data that is critical to evaluating a product's efficacy and safety has to be of sufficient quality and reliability to ensure a valid Analysis.However, past a certain point, the law of diminishing returns applies.
- As trial data approaches "perfection," it becomes Increasingly laborious and expensive to gather and validate additional information. At the same time, the incremental improvement.

Enter Quality By Design

If setting a rigid goal of an absolutely flawless study turns out to be neither realistic nor desirable, how can we ensure that clinical trials Are fine-tuned to provide trustworthy answers to clinical questions and protect patient safety? The answer lies in how we define quality Itself in the context of research[3]. The concept of quality by design (QbD) was first described by engineer and management consultant Joseph M. Juran in the early 1990s.Put simply, it defines quality as freedom from errors that matter.

- For a clinical trial, this could mean errors in study conduct or Inaccuracies in data collection and reporting that affect the prespecified study endpoints (and therefore harm study validity) or that Jeopardize a patient's rights or safety.
- By clearing away the "underbrush" of less important considerations and focusing on essential Elements, trials can be designed to yield more reliable data about the outcomes of interest – and to do so more efficiently.

2.2 Quality by Design (QbD) in Clinical Trials – Build Bullet-Proof Protocols

Making QbD Work In Practice

Implementing QbD can sometimes be an uphill battle In our experience, significant roadblocks can emerge at the outset when justifying The additional time and effort needed for successful implementation [4]. The single biggest challenge to employing QbD may be overcoming Institutionalized reluctance to use a more targeted quality assurance/risk management approach. For these reasons, it is critical to adapt QbD principles in ways that match the needs of the particular trial and its stakeholders

- In Addition, for study sponsors, there should be an organizational commitment to and investment in QbD that is reflected in both Infrastructure and process.
- Resources such as CTTI's QbD Toolkit may prove useful for overcoming hurdles.
- The capacity to analyse and Visualize data that will allow a study team to assess progress, identify gaps or shortcomings, and compare outcomes is also essential to Success. CTTI is currently working to develop additional resources that can support adopters as they move from theory and concept to Implementation [5]. These efforts include the creation of a how-to guide for implementing QbD in clinical trials. Remember: QbD is not one-size-fits-all. Rather, it is a way of approaching trial design and implementation that ensures that each Individual trial is more efficient, more reliable, and — ultimately — more impactful.

3 RECOMMENDATIONS AND DISCUSSION

3.1. Recommendations

- Successful clinical trials consist of a well-designed protocol, robust site-based research infrastructure, and well-qualified site teams[6].
- Therefore, these recommendations on investigator qualification should be used in conjunction with CTTI's Quality by Design recommendations on protocol development and CTTI's Investigator Community recommendations for a holistic approach to conducting quality clinical trials.
- The recommendations presented below are divided into two stakeholder groups: 1) sponsors and CROs, and 2) investigators and their delegates.

3.2 Expand qualification of investigators and delegates beyond GCP training

GCP principles are critical to the reliability and accuracy of trial data and the protection of human subjects. However, repetitive didactic presentation of GCP principles is unlikely to either adequately prepare an inexperienced member of a site team or add value to the practice of an experienced researcher [7] CTTI's recommendations on GCP Training for Investigators [14] describe how to optimize GCP training for members of a site team who may need education about applying GCP elements to conduct quality protocols. Investigators and delegates who regularly demonstrate proficiency in applying GCP elements may be exempted from further GCP training requirements, while still benefiting from protocol-specific training.

4. TOOLS OF QBD

- The concept of QBD has two components -the science underlying the design and the science of manufacturing .
- upon understanding the elements of Q - +D and the steps for QBS implementation ,it is important to be familiar with the commonly used tools in QBD ,including risk assessment ,design experiment (DOE), and process analytical technology.

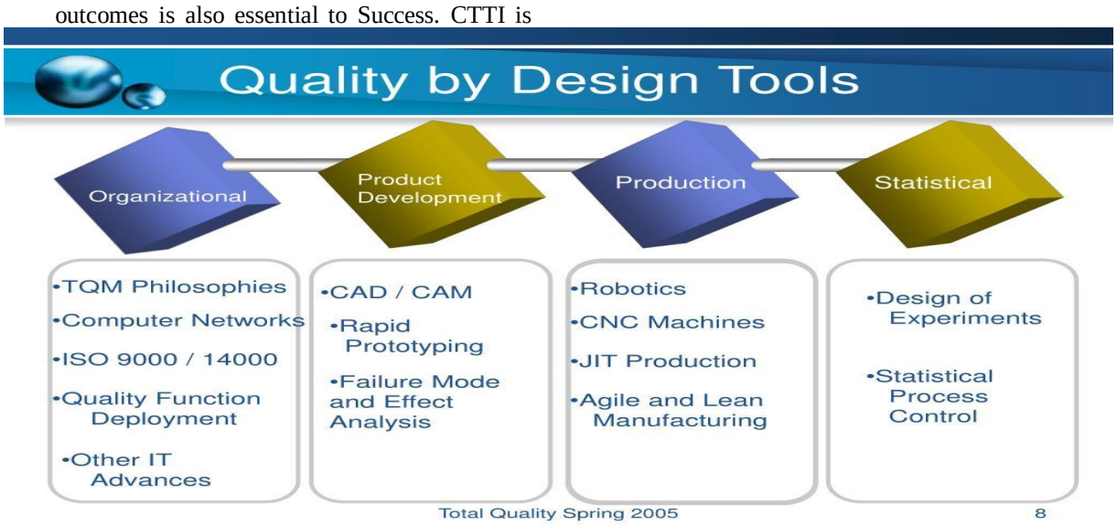

Fig 7: Tools of QBD

4.1 Quality monitoring of QBD

The process is often associated with other quality improvement tools like lean and six sigma. While quality by design features many of the same principles, its focus is on delivering a new product or process that meats customer needs with minimal errors or defects. Ultimately, Lean and six sigma set to correct existing flaws, while QBD prevents these flaws from occurring in first place .quality by design is meant to incorporate quality into the product from the very beginning and achieve long standing customer loyalty[8].The international guidelines behind QBD were first introduced in the pharmaceutical industry between 2009 and 2012.These guidelines define Quality by Design as "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. Quality by design benefits both the customer (who values safe and effective products) and the manufacture(for whom quality and costs will be better understood and more predictable with a QBD approach).

- The process is important because Life Sciences organizations face a number of challenges in the early stages of developing a new product.
- These may include gaps between the:
- Manufacturer's understanding of the customer's needs and the customer's own understanding.
- Manufacturer's understanding of the customer's needs and the actual product design.
- Product design and the final execution of the product. We've all been there. And while these challenges are perfectly natural, QBD can help mitigate them.
- Quality by Design helps to close gaps such as cost and time overruns, failure to reach sales targets, unhappy customers, and even abandoned or delayed development time frames.
- Combined with Process Analytical Technology (PAT) tools, QBD promotes process control while ensuring the product quality attributes are achieved to the highest standard. (A reminder that PAT is a system for designing, analyzing, and regulating manufacturing by measuring the quality and performance attributes of all materials and processes).

4.2 The elements that compromise QBD include:

- Quality target product profile (QTPP)
- Critical Quality Attributes (CQAS)
- Critical Material Attributes (CMAs) Together, the QTPP and the CQAs serve as key performance indicators (KPIs)
- A risk-based approach, manufactures must examine the root cause behind any possible deviation from these KPIs, and identify the CPPs that may be causing the deviation.
- To do so, manufactures must also build a knowledge space and foster an open dialogue around how the QTPP, CMAs, and CPPs are interconnected.

4.3 Outcomes of QBD

- Eliminate batch failures
- Minimize deviations and costly investigations
- Avoid regulatory compliance problems
- Empowerment of technical staff
- Efficient, agile, flexible system
- Increase manufacturing efficiency, reduce costs and protect rejections and waste
- Build scientific knowledge base for all products
- Better interact with industry on science issues
- Ensure consistent information
- Incorporate risk management
- Reduce end-product testing
- Speed-up release decision

5 RISK ASSESSMENT

Risk assessment is a systematic process of organizing information to support a risk decision to be made within a risk Management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with Exposure to those hazards. It is the first step of quality risk man assessment process; the other two steps are risk control and risk [9]. Risk control includes decision making to reduce and/accept risks. The purpose of risk control is to reduce the risk to an acceptable level at the final stage, the output/results of the risk management process should be reviewed to take into account new knowledge and experience. Throughout the risk Management process, risk communication, the sharing of in Formation about risk and risk management between the parties (including regulators and industry, industry and the patient, within a company, industry or regulatory authority, etc.), should be ongoing at any stage of the risk management process. The Included information might relate to the existence, nature, form Probability, severity, acceptability, control, treatment, detect ability or other aspects of risks to quality.

5.1Errors in clinical trials

5.1.1Engage stakeholders

- The management and operations of a clinical trial involves many different stakeholders.
- Communication to various groups should be targeted and clear.
- To the executive team, the focus may be on cost optimization and avoidance of risk [10]. Conversely, communication with monitors may be focused on how the new RMB approach will require key critical thinking and analysis in addition to traditional site management that may be done remotely, which could provide increased quality of life due to reduction of time on the road.
- Setting clear expectations and defining ownership of tasks with vendors, like CROs, during implementation will ensure roles and responsibilities are understood from the outset.
- Even prioritization of maturity and experience during site qualification and selection can help bring success.
- Across all groups, setting the realistic expectation that refining the monitoring process is a calculated change that may cause some immediate disruption is important, but change will provide long-term efficiencies and higher quality data.
- It's also important to set the precedent that there will be bumps in the road, but "stick with it," as opposed to seeing those bumps as an invitation to revert to the old ways.

5.1.2 Incremental change

It is not expected that sponsors will make an immediate shift from a traditional monitoring process to a risk-based approach overnightt. Sponsors are encouraged to start with a smaller, incremental adoption of one or more of the principles of RBM [11] Operations teams can then showcase lessons learned as evidence of success, and in effect, this will convince stakeholders to stick with this approach. This could be as simple as engaging new but already

existing technology and tools that would align with planned or active protocols studies like e Source, e Consent, central monitoring, direct data capture, or EMR access. Or more complex changes like transitioning interim monitoring visit (IMV) schedules to be dependent on metrics such as completed patient visits instead of relying on a preset IMV schedule of every 6 weeks, for example. CRAS will then be on site when there is an appropriate volume of data to be verified.

5.2 Incorporate Risk Management

Start with a robust risk assessment to identify and define risk. This includes defining critical processes and critical data (primary and secondary endpoints, safety, and other critical variables) and identifying the thresholds for when action is needed [12]. These standards are then used to inform study plans across functional areas to define when action should be taken and what specifically that action should be. Simply put: Set the standard, make sure it's documented, and ensure the standards are followed.
Rethinking monitoring and monitor training

Sponsors need broader 'thinking about monitoring' and monitor training. Monitoring is no longer just on-site, "boots on the ground" SDV, but entails more active data review between visits. With robust training and on boarding, monitors will be called upon to evaluate quality of data and trending analysis during centralized review that requires a shift in core competencies to include more critical and strategic thinking. On-site visits will be more focused on other tasks like drug accountability, addressing enrolment challenges, assessing protocol compliance, and building relationships instead of 100% SDV of every data point.

Start early in the development process

Where possible, setting the stage early in the design process allows for protocol development to be streamlined and focused on what matters most for a specific trial. Focusing on the initial question of "How much data do you need to see to be comfortable that the study data is accurate?" can help make clear which study activities are essential to patient safety and credible study results and eliminating nonessential activities. QBD is a process for designing and launching new products. In the Life Sciences space, these products may include pharmaceuticals, medical devices, software solutions, and other relevant tools. The idea is to create a high-quality product that meets the customer's needs while reducing risk for the manufacturer.To this end, a key objective of QBD is to make sure all variability is identified, justified, and addressed before the product goes to market. The goal here is for the end product to meet its predefined characteristics from the very beginning, by eliminating errors and other discrepancies.

6 CURRENT SCENARIO OF QBD IN PHARMACEUTICAL PRODUCT

- Quality by design (QBD) encourages the pharmaceutical industry to use risk management and science-based manufacturing principles to gain process and product understanding and thus assures quantity of the product [13].
- with the objective to curb the rising costs for development and regulatory barriers to innovation and creativity, QBD is being widely promoted by food and drug administration (FDA)and International Conference on Harmonization (ICH).
- This describes the elements, different design and tools of (QBD) as well multidimensional applications of QBD ranging from dosage form and method development to meeting latest regulatory requirements.
- The understanding of a process is facilitated by proper identification of sources of variation, management of variability by process design, and prediction of product quality attributes using design space.
- The pharmaceutical industry is rapidly adopting the QBD principles of fabrication of safe, effective and quality products; however, we are still on the journey and the process of gathering all experience and metrics required for connecting and demonstrating QBD benefits to all stake holders is still in progress.
- Understanding the formulation and process parameters with philosophy of QBD will be useful for the optimization of complex drug delivery systems in the near future.

7. CONCLUSION:

Quality drug products with desired pharmacotherapeutic effects for the treatment available in pharmaceutical markets. The tools od QbD like lean and sigma in pharmaceutical manufacturing initiative the improvement in standards of products life cycle. In assessment of risk process identification of hazards and the analysis to those hazards should be reviewed into account in aspect of risks to assure the quality of product.

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