



QUALITY BY DESIGN (QBD): A QUALITY IMPROVEMENT PERSPECTIVE FOR PHARMACEUTICAL DEVELOPMENT



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IJPRBS-QR CODE

PAPER-QR CODE

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Accepted Date:

16/05/2013

Publish Date:

27/06/2013

Keywords

Quality by Design (QbD),
Target Product Profile
(TPP),
Critical quality attributes
(CQA),
Design Space,
Control Strategy,
Product lifecycle

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Abstract

Quality by design (QbD) is a new modern perspective towards the qualitative pharmaceutical development. This is a systemic approach to design and development of the pharmaceutical formulations and manufacturing processes that ensures the predefined product quality. This QbD consists the chain of elements which on execution gives the consistent quality over time. Implementation of QbD enables the assurance of pharmaceutical quality by understanding and controlling formulation and manufacturing variables. Quality risk management (QRM) serves the base for control strategy, which is only can attain by process understanding. This new paradigm of drug development provides relief from regulatory framework that imparts flexibility, increase in efficiency by offering important benefits by business point of view throughout the product's life cycle. Continual improvement can be achieve by QbD implementation as it is systematic way of product and process development.

INTRODUCTION:

ICH Q8 defines quality as “The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity.” A frequently used definition of quality is “Delighting the customer by fully meeting their needs and expectations”¹. These may include performance, appearance, availability, delivery, reliability, maintainability, cost effectiveness and price. i.e. Total customer satisfaction. Quality starts with market research to establish the true requirements for the product or service and the true needs of the customers. So, at this stage the focus of quality is on the end product.² However, for an organisation to be really effective, quality must span all functions, all people, all departments and all activities and be a common language for improvement.³

**What is next for 21st Century: -----
- QbD?**

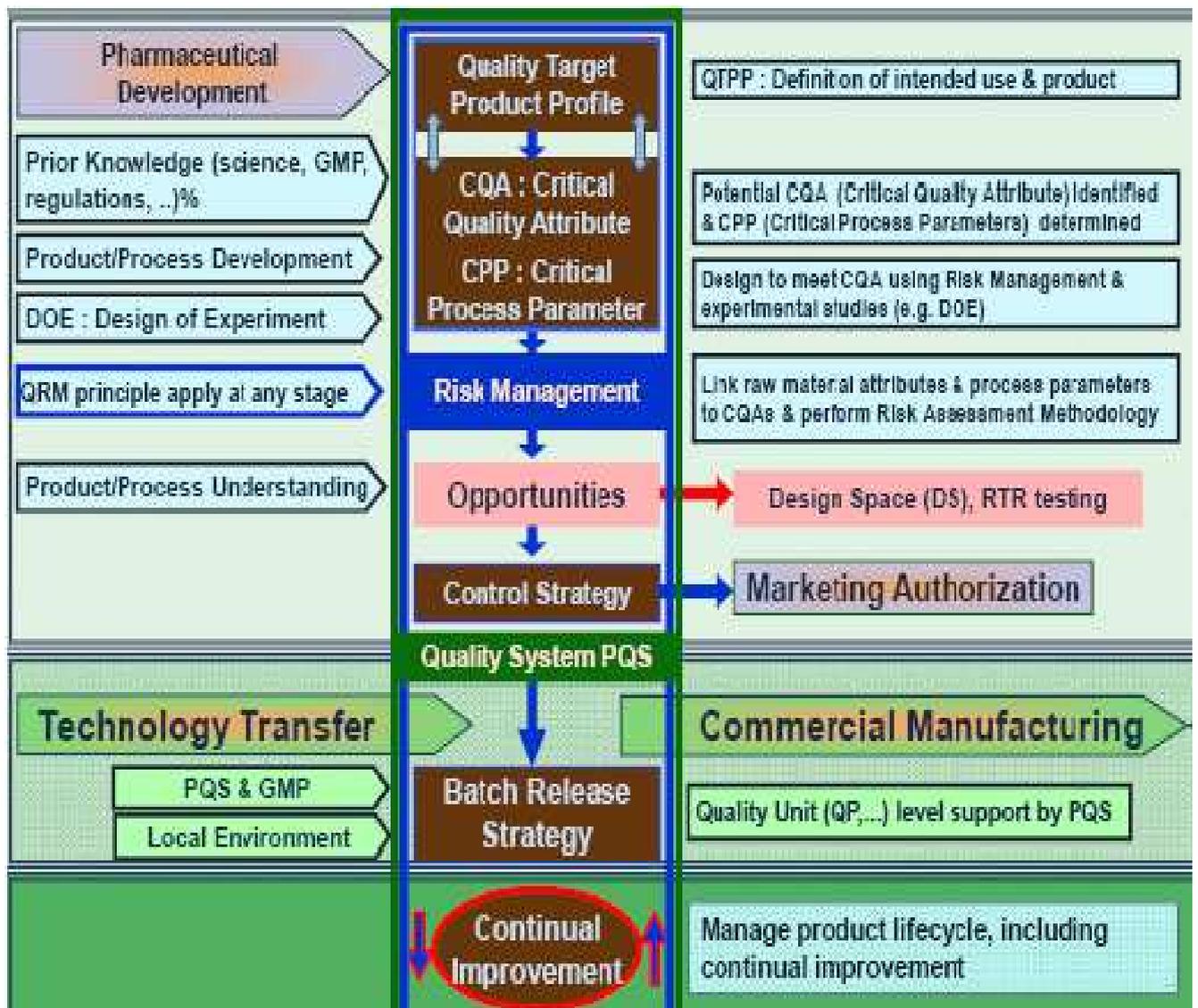
What is Quality by Design (QbD)? Quality by Design (QbD) is a concept first outlined by well-known quality expert **Joseph M. Juran** in various publications, most notably Juran on Quality by Design. Juran believed

that quality could be planned, and that most quality crises and problems relate to the way in which quality was planned in the first place. While Quality by Design principles have been used to advance product and process quality in every industry, and particularly the automotive industry, they have most recently been adopted by the U.S. Food and Drug Administration (FDA) as a vehicle for the transformation of how drugs are discovered, developed, and commercially manufactured. This FDA imperative is best outlined in its report “Pharmaceutical Quality for the 21st Century: A Risk-Based Approach. In the past few years, the Agency has made significant progress in implementing the concepts of "Quality by Design" (QbD) into its pre-market processes. The focus of this concept is that quality should be built into a product with a thorough understanding of the product and process by which it is developed and manufactured along with a knowledge of the risks involved in manufacturing the product and how best to mitigate those risks. This is a successor to the "quality by QC" (or "quality after design") approach that the companies have taken up until

1990s^{4,5}. The QbD initiative, which originated from the Office of Biotechnology Products (OBP), attempts to provide guidance on pharmaceutical development

to facilitate design of products and processes that maximizes the product's efficacy and safety profile while enhancing product manufacturability^{6,7}.

Key steps for a product under quality by design (QbD)



• QUALITY

– Acceptably low risk of failing to achieve the desired clinical attributes

• PHARMACEUTICAL QUALITY

= f {drug substance, excipients, manufacturing.}

• QBD

– ‘Product and process performance characteristics scientifically designed to meet specific objectives, not merely empirically derived from performance of test batches’⁸

Table 1

Current Vs QBD approach to pharmaceutical development

Current Approach	Qbd Approach
1. Quality assured by testing & inspection.	1. Quality built into product & process by design, based on scientific understanding.
2. Data intensive submission disjointed information without “Big Picture”.	2. Knowledge rich submission showing product knowledge & process understanding.
3. Specification based on batch history.	3. Specifications based on product performance requirement.
4. “Frozen process” discouraging changes.	4. Flexible process within design space, allowing continuous improvement.
5. Focus on reproducibility-often avoiding or ignoring variation.	5. Focuses on robustness-understanding & controlling variation.

BACKGROUND OF QUALITY BY DESIGN:

Quality by design (QbD) is the concept first developed by the famous quality expert named Joseph M. Juran in his 1992 book called "The New Steps for Planning Quality in to Goods and Services". He believed that quality could be planned in the very first stage of the production rather than final testing. In other words, we can say that the computer we use, the phone we answer, the airplane we ride, the car we drive and the camera we use are all products of Quality by Design but we cannot say that whatever tablet we ingest and whatever biologics we use are the products of Quality by Design.^{9,10}

In 1990s, many of the medical device manufacturing company has implemented Quality by Design aspect which resulted in reduced risk and manufacturing cost and at the same time increased patient safety and product efficacy. From the success of QbD aspect in medical device manufacturing, the FDA officials felt that this concept has to be applied to drugs and biologics also. With the huge help of some pharmaceutical companies, pilot programs were started to share the Quality by Design application and

process understanding with the other companies.¹¹

"The FDA publication defined Quality by Design as:

- Developing a product to meet predefined product quality, safety and efficacy; and
- Designing a manufacturing process to meet predefined product quality, safety and efficacy."¹²

ADVANTAGES ¹³

- ✓ Better innovation due to the ability to improve processes.
- ✓ More efficient technology transfer to manufacturing.
- ✓ Less batch failures.
- ✓ Greater regulator confidence of robust products.
- ✓ Risk- based approach and identification.
- ✓ Innovative process validation approaches.
- ✓ For the consumer, greater product consistency.

- ✓ More product availability and less failures / rejections.
- ✓ Improved yields, lower lost, fewer investigations, reduced testing etc.

PHARMACEUTICAL QUALITY BY DESIGN:

Quality in pharmaceuticals is very much important since it directly deals with patient's health and so Food and Drug Administration (FDA) has set stringent law for drug approval. It is a U.S. agency that has power to approve or reject the drug product, biological or medical devices in order to set the Americans free from risk. Along with the dosage forms, it is also concerned about the drug development process e.g. how it is manufactured and purity of the condition under which it is manufactured.¹⁴

In order to produce quality product consistently, FDA suggests the pharmaceutical Industries to implement Quality by Design (QbD) concept. Pharmaceutical QbD is FDA's one of the two systemic, holistic and risk based approach to pharmaceutical development. The other one is PAT (Process Analytical Technology). If QbD explains "what to do," then PAT is a framework for "how to do". QbD is

overarching philosophy articulated in both the cGMP regulations and in robust modern quality system.^{15,16}

The principle of QbD is "Quality should be built in design", the testing alone cannot give surety on product quality. It means that designing the whole drug development and manufacturing process in such a way that produces product with pre defined quality objective. QbD identifies characteristics that are critical to quality from the perspective of patients, translates them into the attributes that the drug product should possess, and establishes how the critical process parameters can be varied to consistently produce a drug product with the desired characteristics. In order to achieve this, the relationships between the formulations and manufacturing process variables and product characteristics are thoroughly understood and source of variability should be identified. This knowledge and skills are then used to implement flexible and robust manufacturing process that can adapt and produce consistent quality product over a period of time.¹⁷

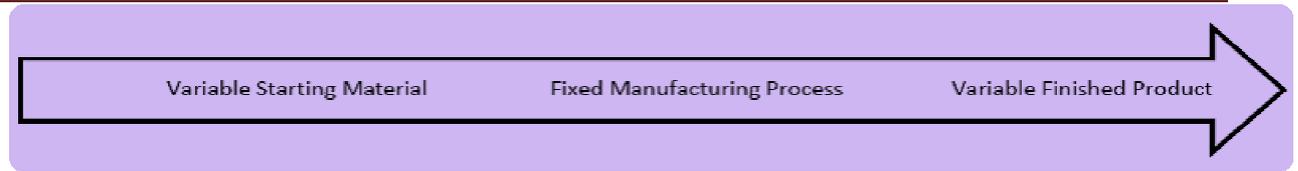
Thus some of the **important QbD features** include:

- Define Product quality profile
- Design and develop Manufacturing Processes
- Identify and control the critical control parameters, Critical quality attributes and source of variability.
- Control the whole manufacturing process to produce quality product consistently over a period of time.

QUALITY BY TESTING VS QUALITY BY DESIGN (QbT VS QbD) ¹⁸

Quality by testing is the approach that most of the pharmaceutical organizations are using currently. Some of the companies has replaced QbT concept to QbD to produce a quality product consistently. In Quality by Testing, the final product is tested to get assurance that particular batch product is within the specification and is of highest standard quality.

The recent approach is QbT where if drug substance and excipients meet the specification the next step of unit operation is carried out such as Mixing, blending, drying, compression, coating etc. with fixed process parameters. If the materials do not meet the In Process Specifications then the material is discarded. If it passes, then an assay is performed where the % of purity, Dissolution, Disintegration, Moisture content is measured. In those cases, the acceptance criteria based on one or more of the batch data. Finally, if product fails to meet the finished product specification requirement, it is discarded. This is how pharmaceuticals are manufactured using QbT approach. In Quality by Design, Consistency in quality product manufacturing comes from the designed and control of the process. The next step is not performed until the step before that gets pass. If the first step fails then the root cause of the failure is investigated and understood to fix it in order to move on to subsequent steps.



Traditional Manufacturing Process

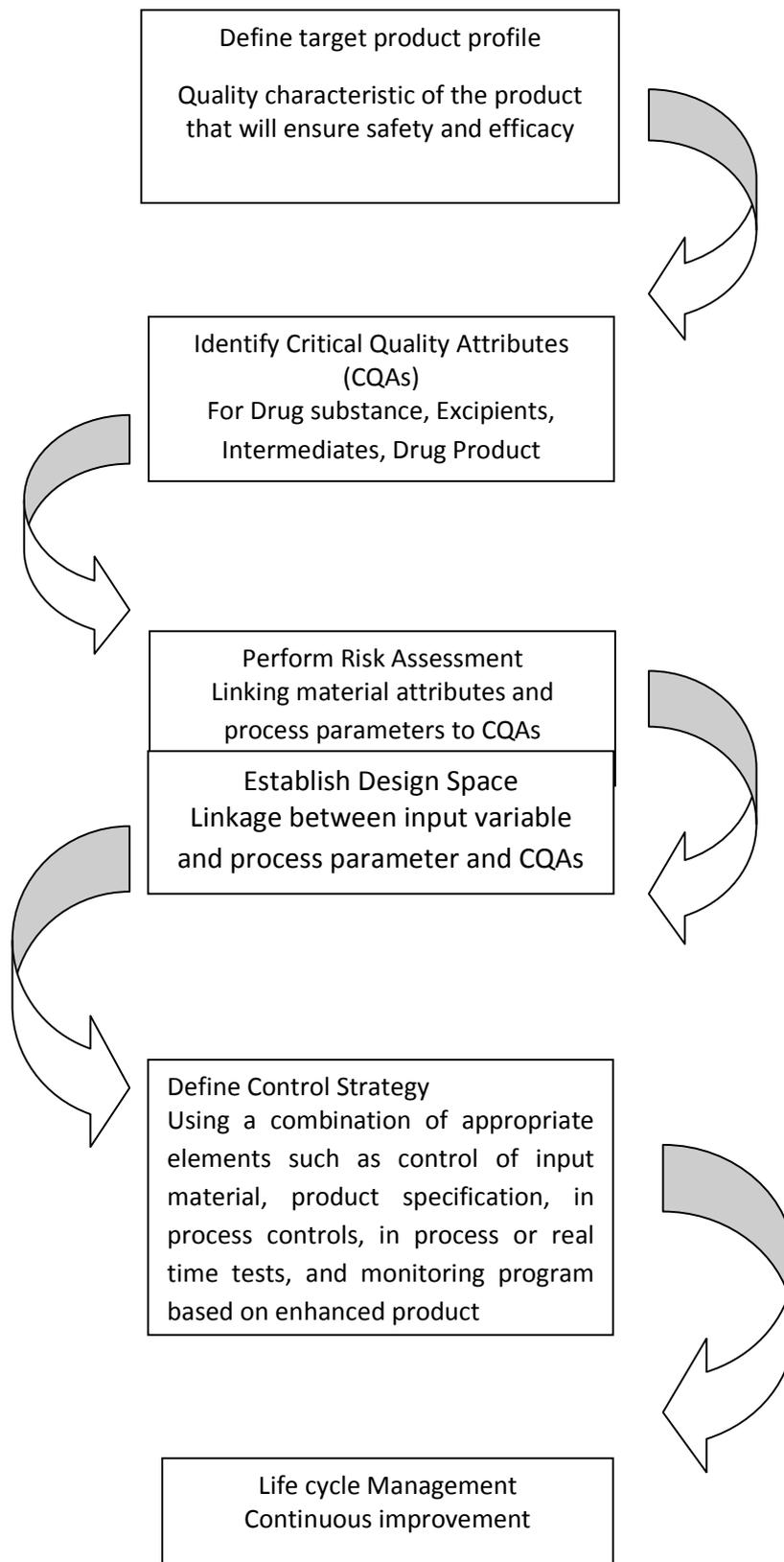


Quality by Design (QbD) Manufacturing Process

Fig. 2: Comparison of Quality by end product testing and Quality by design

ELEMENTS OF QUALITY BY DESIGN (QBD) APPROACH¹⁹

QbD development process includes the following elements that accomplish the following steps as per fig. 1



QUALITY BY DESIGN (QBD) STEPS:

- a) To define the Target Product Profile
- b) Determination of raw material Critical Quality Attributes (CQAs)
- c) To establish the relationship between the drug and excipient attributes and the process parameters to the Critical Quality Attributes
- d) To define the Design Space
- e) Define the Control Strategy
- f) Product lifecycle management & continual improvement

BUILDING BLOCKS OF QBD ²⁰

The first step to implement Quality by Design is to understand critical output of QbD and after that identify critical building blocks of QbD such as improving process understanding and risk associated with it.²⁰

- **Critical Quality Attributes (CQAs):**

The critical process output measurements linked to patient needs. A CQA is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product

quality. CQAs are generally associated with the drug substance, excipients, intermediates (in-process materials) and drug product.

CQAs of solid oral dosage forms are typically those aspects affecting product purity, strength, drug release and stability. CQAs for other delivery systems can additionally include more product specific aspects, such as aerodynamic properties for inhaled products, sterility for parenterals, and adhesion properties for transdermal patches.

For drug substances, raw materials and intermediates, the CQAs can additionally include those properties (e.g., particle size distribution, bulk density) that affect drug product CQAs. Potential drug product CQAs derived from the quality target product profile and/or prior knowledge are used to guide the product and process development. The list of potential CQAs can be modified when the formulation and manufacturing process are selected and as product knowledge and process understanding increase.

Quality risk management can be used to prioritize the list of potential CQAs for

subsequent evaluation. Relevant CQAs can be identified by an iterative process of quality risk management and experimentation that assesses the extent to which their variation can have an impact on the quality of the drug product.²⁰

- **Critical Process Parameters (CPPs):** The process inputs (API, Excipients), process control and environmental factors that have major effects on the Critical Quality Attributes (CQAs).
- **Design Space:** The combination of input variables and process parameters that provide quality assurance.
- **Failure Mode and Effects Analysis (FMEA):** It examines raw material variables, Identifies how a process can fail and the areas of process that remains at greatest risk of failing.
- **Process model:** Quantitative pictures of process based on fundamental and statistical relationship that predict the critical quality attribute (CQA) result.
- **Process Capability:** It tracks process performance relative to CQA specification and provide measurement

repeatability and reproducibility regarding CQAs.

- **Process Robustness:** The ability of process to perform when faced with uncontrolled variation in process, input and environmental variables.
- **Process Control:** It is a control procedures including statistical process control that keeps the processes and measurement system on target and within desired variations.
- **Raw material factors:** It includes the stability and capability of raw material manufacturing processes that affect process robustness, process capability and process stability.
- **Risk level:** It is a function of the design space, FMEA result and process and measurement capability, control and robustness.
- The output of process control, design space and risk are consistent with this approach. The building blocks needs to be assembled as mentioned below before results can be realized.
- Identify Critical Quality Attributes

- Characterize raw material variation
- Identify Critical Process Parameters
- Characterize design Space
- Ensure process capability, process control and process robustness
- Create process model monitoring and maintenance and Offers risk analysis and management

QUALITY BY DESIGN ACROSS THE PRODUCT LIFESPAN

1. DEVELOPMENT STAGE:

New drug development stage is riskiest and costliest stage of the drug and biologic life span. If Quality by Design concept is well understood and well applied, it provides most powerful results such as reducing time, cost, risk and efforts. John Avellanet said that "Quality by Design is a strategic and systemic approach to get the new product pipeline to market faster, easier and for less."²¹

▪ **PRECLINICAL:**

Quality by Design improves product development if we use our prior knowledge from the previous experience, previous product or from

literature surveys. We can identify and specify the characteristics that our new product must possess from the previous experience and customer needs.

▪ **NONCLINICAL:**

To meet the pre determined specifications, a company must conduct preclinical as well as nonclinical experiment to verify the ability of the product being developed to meet the targets. In other words, a company should carry out in vivo and in vitro tests and depending on the product; the amount of active molecule in serum has been drawn from the feasibility experiment.

▪ **CLINICAL:**

The clinical studies are confirmatory if we apply Quality by Design concept during drug development. A company can use the traditional approach to the clinical trials or try adaptive trial. During the drug development process, when the product reaches to the phase III trial stage a company must focus only on the micro refinements to their process as well as their manufacturing process.

▪ **SCALE-UP:**

The scale-up is defined as conversion of an industrial process from a pilot plant or a small laboratory set up to a large commercial manufacturing. It is also a part of Quality by Design. Application of QbD during scale up allows us to document changes and rationale during conversion from pilot plant manufacturing to full scale manufacturing.

For example, imagine that Stevens Pharmaceuticals limited is actively engaged in chlorpromazine tablet manufacturing. The pilot model was successful. Now the company wants to switch the pilot model to a large commercial manufacturing. During the coating of the tablet the company need increased nozzle size on a sprayer so that they can meet the higher spray rate for faster manufacturing. As long as the larger nozzle size maintained the same droplet size as in pilot production, then no further testing and validation would be required. Such information is then documented and attached in the final submission for market approval.

▪ **SUBMISSIONS FOR MARKET APPROVAL:**

"Submissions based on QbD have more scientific information on product, process and controls which allows faster reviews" According to FDA's own internal analysis, Quality by Design based applications are processed 63% faster than traditional submissions.

2. MANUFACTURING:

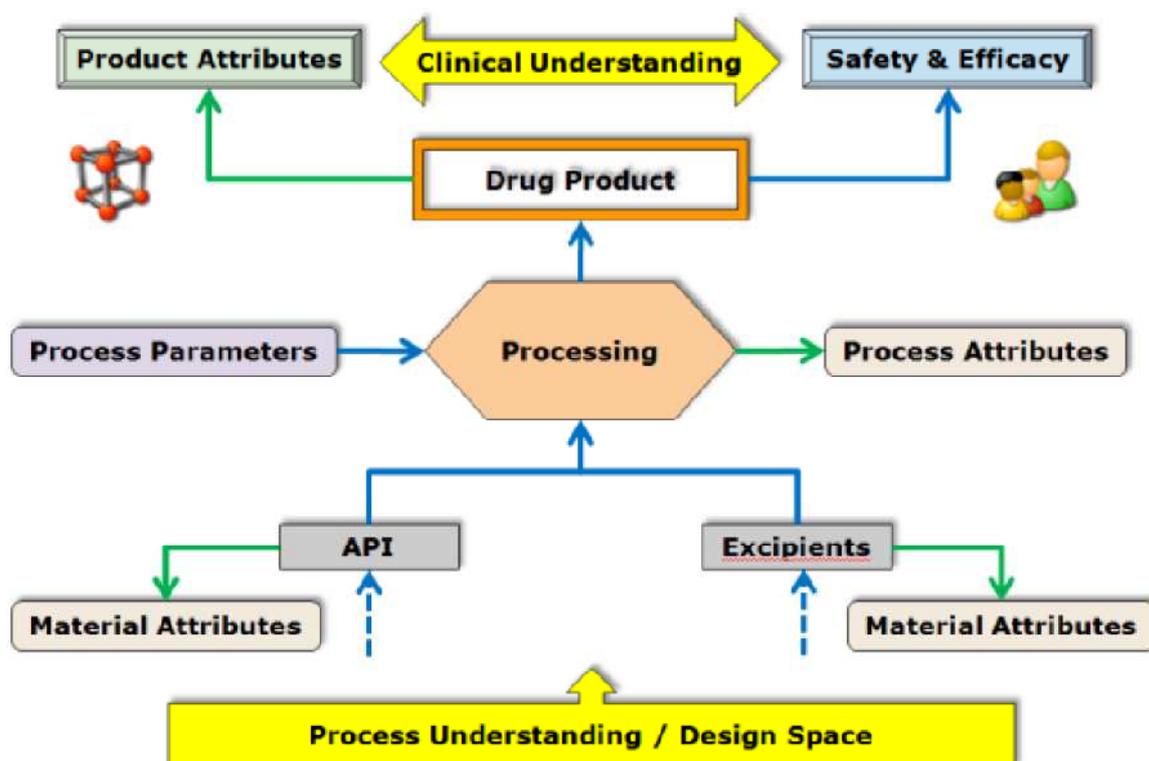
When Quality by Design concept applied to drugs and biologics manufacturing, it offers more business flexibility. Once upon a time, it was quite a bit difficult for the companies if they want to modify their manufacturing process. In those cases, they have to wait for the regulatory approval prior to implementing changes. But now, under QbD, this review can be eliminated by relying on design space, Process Analytical Technology and 'Real Time' quality control.

• **DESIGN SPACE:**

After CQAs for a product have been identified, the next step is to define the product design and design space (that is, specifications for in-process, drug substance

and drug product attributes). Product manufacturing processes that do not impact final product quality, its safety and efficacy are called "design space" As per the ICH guidelines the design space is "the multi dimensional combination and interaction of input variables (e.g. material attributes) and process parameters that have been

demonstrated to provide assurance of quality". "Design Space consists of the set of all values and combination of the controllable factors that are predicted to yield all of the output quality attributes within their allowable ranges with a sufficient high level of assurance"²²,

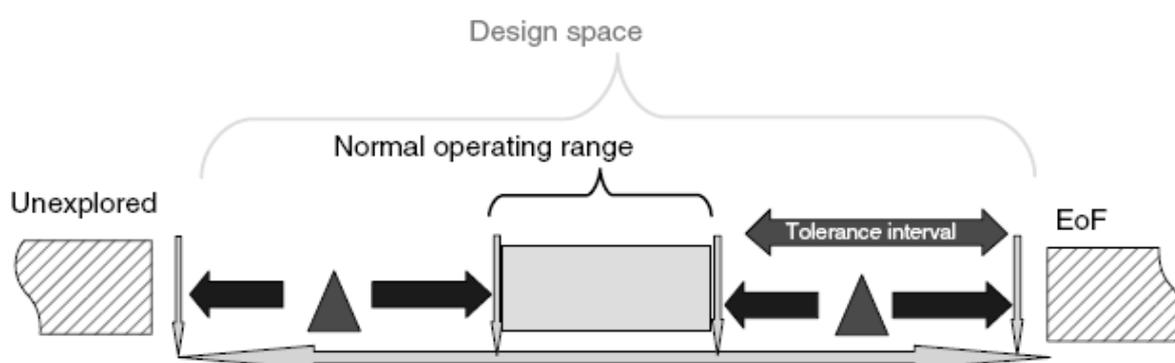


These specifications are established based on several sources of information that link the attributes to the safety and efficacy of the product, including, but not limited to, the Published literature on other similar products, Process capability with respect to the variability observed in the

manufactured lots, Design space, Clinical and nonclinical studies with similar platform products. The difference between the actual experience in the clinic and the specifications set for the product would depend on our level of understanding of the impact that the CQA under consideration

can have on the safety and efficacy of the product. In QbD, an improved understanding of the linkages between the CQA and safety and efficacy of the product is required. QbD has brought a realization of the importance of the analytical, nonclinical and animal studies in establishing these linkages and has led to the creation of novel approaches. In order

to design and develop a robust generic product that has the desirable TPQP, a product development scientist must give serious consideration to the biopharmaceutical properties of the drug substance. These biopharmaceutical properties include physical, chemical, and biological properties²³



Design space with an edge of failure (EoF) and use of tolerance interval to mitigate risk.

- **KNOWLEDGE SPACE:**

Movement within design space does not considered a change and so it does not require regulatory review but movement out of the design space is considered change and requires regulatory review or approval. The more we know about the impact of the process on the product's final

quality and safety, the more flexibility a company can have under quality by design.²⁴

- **PROCESS ANALYTICAL TECHNOLOGY (PAT):**

Achieving QbD may involve the use of instruments more sophisticated than those currently used in pharmaceutical manufacturing processes. Some of these instruments have been used for decades in other industries, but have not yet been

applied to pharmaceutical production processes. Some of the newer instruments available to life science manufacturers make relatively simple measurements like effusivity. Other instruments make much more complex measurements like Near Infrared (NIR) absorption. In many cases, these instruments are capable of measuring the CPPs and CQAs in real-time. Such instruments generate large amounts of data that must be understood if the measurements are to be useful.

The usefulness of any PAT or other process improvement initiative in QbD depends on all the data (discrete, replicate, continuous and paper-based) and the right process trending, reporting, descriptive analysis, univariate and multivariate cause-and-effect analysis, and parameter relationship modeling capabilities all being easily available on-demand to users in the same integrated environment. Users must be able to work with continuous, discrete and replicate data together for quantitative analysis. It is very difficult to predict the effect of process change on final product. An essential part of quality by design accepts that even if the effect of process change cannot be predicted, it can be fully

monitored and controlled. Process analytical technology allows us to continuously monitor, test, analyze and adjust whole manufacturing process to increase control and improve efficiency through the measurement of critical process parameters (CPP) which affects critical quality attributes (CQA).²⁵

- **"REAL-TIME" Quality Control:**

The third aspect of Quality by Design in the manufacturing arena is the ability to shift quality control upstream in to production. By this way we can reduce the waste and the cost of producing a batch that ultimately fail the quality control. By embedding quality control checks throughout manufacturing process, Quality by Design allows us to increase our production, improve our product and streamline the whole process.²⁶

3. CONTROL STRATEGIES:

A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug-product materials and

components, facility and equipment operating conditions, in-process controls, finished-product specifications, and the associated methods and frequency of monitoring and control.

Specifically, the control strategy may include:

- Control of input material attributes (e.g., drug substance, excipients, primary packaging materials) based on an understanding of their impact on processability or product quality.²⁷
- Product specifications
- Procedural controls
- Facility controls, such as utilities, environmental systems and operating conditions
- Controls for unit operations that have an impact on downstream processing or end-product quality (e.g. the impact of drying on degradation, particle size distribution of the granulate on dissolution)
- A monitoring program (e.g., full product testing at regular intervals) for verifying multivariate prediction models.

The Control Strategy should establish the necessary controls - based on patient requirements - to be applied throughout the whole product lifecycle from product and process design through to final product, including API and Drug Product manufacture, packaging and distribution. Embedding quality control checks throughout manufacturing process is one of the control strategies that helps ensure production quality. We all know that Quality by Design is simply designing and developing the product and manufacturing process in order to get predefined product quality, safety and efficacy. If we link the product design and development stage directly with process development then it gives us the degree of control required.²⁸

CONTINUOUS IMPROVEMENT:

“Continuous improvement is an essential element in a modern quality system that aims at improving efficiency by optimizing a process and eliminating wasted efforts in production. These efforts are primarily directed towards reducing variability in process and product quality characteristics.”²⁹

QbD focuses on building quality into the product and manufacturing processes, as well as continuous process improvement – reduction of variability. The backbone for Continuous Improvement is the Pharmaceutical Quality System. PQS should facilitate continual improvement and help to: “Identify and implement appropriate product quality improvements, process improvements, variability reduction, innovations and pharmaceutical quality system enhancements, thereby increasing the ability to fulfill quality needs consistently. Quality risk management can be useful for identifying and prioritizing areas for continual improvement. “Continuous improvement is not the same as corrective actions preventative actions (CAPA). CAPA’s occur when product quality characteristics are in question (e.g., out of specification). For continuous improvement efforts, products should already be in compliance with their specifications and process improvement steps should be within the original "design space”³⁰

Examples of Continuous Improvement include adjusting a set point of a process, advanced control techniques ,new equipment of the same design, re-designing

a process step ,changing a working process, LEAN initiatives, simplifying documents, automatic a process, installing on-line measurements, removing a unit operation, changing the design space and updating the Control Strategy .³¹

Data for continuous improvement include OOS-OOT data, Manual batch record data, Raw material data Process analyses data, Process equipment data, Data from other sites, Customer complaint data, Drug product data, Data from historians and Quality data from LIMS.

A If we remember back on the definition of Quality by Design as "everything we do to directly promote and prove safety, efficacy and quality of our product," then continuous improvement is a part of promoting and proving safety, efficacy and quality of our product. By continuous improvement, we can focus on making the whole manufacturing process efficient without negatively impacting the product. Since QbD facilitates continuous improvement in product quality it increases the regulatory flexibility.^{32,33}

PRODUCT PERFORMANCE:

Key to successful implementation of Quality by Design is to identify Critical Process Parameters (CPP) and Critical Quality Attributes (CQA) that are critical to safety, efficacy and Quality of the product. If we can prove that drug excipients like food color or sweetening agent has no impact on safety, efficacy and quality of final drug product then we can decide not to bother about testing of those materials. Similarly, those processes that have no impact on product safety, efficacy and quality can also receive minimal attention, testing and control. This undoubtedly reduces the costs involved in product development and its production.^{34,35}

FUTURE PROSPECTIVE OF QUALITY BY DESIGN:

After fully implementation of QbD, one can get assurance that all the critical sources of process variability have been identified, measured and understood so that they can be controlled by the manufacturing process itself. That is why the benefits of QbD are significant. Such as,^{36,37}

- Reduces batch failure rate
- Reduces final product testing

- Reduces batch release cost
- Reduces operation cost from fewer failures
- Increased capability to meet both customer and regulatory needs
- Reduced raw material and finished product inventory costs
- Faster regulatory approval of NDA and process changes
- Fewer and shorter regulatory inspection of production site
- facilitates easier management of technical change
- Maximize profit by increasing purchase intent

These benefits translate in to significant reduction in capital requirement, resource cost and time to value. That is why it is said that it is most misunderstood and misused tools available to pharmaceutical industry but if understood thoroughly and implemented properly, the benefits are enormous

CONCLUSION:

Pharmaceutical quality by design is a systemic approach to the pharmaceutical development which begins with predefined quality objectives. QbD is about using correct tool for specific job. It is a mind set and not a process. QbD works for any process and does not require a 'project'. The only reason why most organization are still thinking about QbD rather than implementing is "Too many other things to do". But if understood and implemented well then it enhances and modernize the regulation of pharmaceutical manufacturing and product quality at the same time offers immense benefits. The results shows that companies who adopt QbD can expect significantly reduced risk of costly deviation and rejects. It also reduces the time required by the FDA to review the NDA submissions 63 % faster. Since it is a FDA's 21st century's risk based approach, any company if understand and implement QbD correctly can build five star quality products and make FDA happy.

"If a screw is loose ----- Tight it ----- Don't rebuild the whole house!"

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