An overview of quality by design engineering essay

Since there is immense competition globally and growing impact of Information technology, the pharmaceutical industry should need to improve its performance. The industry should implement newer technologies that can effectively reduce cost of production and at the same time improves product quality and regulatory compliance. Quality by Design is a newer approach that has been offered by the United States Food and Drug Administration (USFDA) which if understood well and implemented properly can save considerable amount of time and cost and at the same time can improve final product quality and regulatory compliance which can increase the speed of product to reach in to the market. This article discusses the background of quality by design concept, Building blocks of Quality by Design, and its approach across the product life span and benefits that it offers.

Introduction:

In 2002, the U. S. Food and Drug Administration (FDA) published a guidance document for pharmaceutical companies on cGMP for the 21st century. This guidance document expressed a strong desire that companies should build quality, safety and efficacy in to their product. This concept is now known as Quality by Design (QbD).

Till now, the meaning, benefits and impact of quality by design is confusing to many people. Some says that it is a newer way to develop drugs, biologics and devices; some says that it can shorten the production cycle; some says that it provides more business flexibility but no one knows what it is exactly. Some people do not even know that where, when and how should it be

applied? Initially there are so many companies who tried to adopt Quality by Design concept but confusion gave way to frustration.

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. The concept was first used in automobile industry. There is one article published in June 2007 titled " Elucidation: Lessons from the Auto Industry" says that Toyota Automobiles was the first company who implemented many Quality by Design concept to improve their automobiles in 1970s. That is why we can say that Quality by Design concept is new only for FDA regulated industries and not for other industries like technology, aeronautics, telecommunications etc. 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.

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. So, the internal discussion in FDA started in late 1990s and finally they published a concept paper in 2002 on cGMP in 21st

century. 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.

“ 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.”

But still it is one of the most misunderstood and misused tools available to many pharmaceuticals as well as Medical devices company because FDA has just published the paper along with its definition which clarifies FDA’s approach, it left far too many questions unanswered. The companies were left to implement Quality by Design concept on its own. John Avellanet, a consultant from cerulean associations LLC says that “ when Quality by Design is planned and implemented properly, the benefits are enormous. But if Quality by Design is tackled haphazardly, the benefits fizzle.”

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.

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. 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[2]. 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[2]. 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)

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.

Building Blocks of QbD

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.

- Critical Quality Attributes (CQAs): The critical process output measurements linked to patient needs [3].
- Critical Process Parameters (CPPs): The process inputs (API, Excipients), process control and environmental factors that have major effects on the Critical Quality Attributes (CQAs) [3].
- Design Space: The combination of input variables and process parameters that provide quality assurance [3].
- 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 [3].
- Process model: A quantitative picture of process based on fundamental and statistical relationship that predict the critical quality attribute (CQA) result [3].
- Process Capability: It tracks process performance relative to CQA specification and provide measurement repeatability and reproducibility regarding CQAs [3].

- Process Robustness: The ability of process to perform when faced with uncontrolled variation in process, input and environmental variables [3].
- Process Control: It is a control procedures including statistical process control that keeps the processes and measurement system on target and within desired variations [3].
- Raw material factors: It includes the stability and capability of raw material manufacturing processes that affect process robustness, process capability and process stability [3].
- Risk level: It is a function of the design space, FMEA result and process and measurement capability, control and robustness [3].

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
- 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.”

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[3].

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:

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”[4].

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.

Process Analytical Technology (PAT):

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).

“ 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 reduces 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.

3. Control Strategies:

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.

Continuous improvement:

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.

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.

Benefits 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,

- Reduces batch failure rates

- 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 product and make FDA happy.

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

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