Quality by Design Approach: Role in pharmaceutical industry

A THESIS

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By

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Annexure I

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Patents related to API, process, product, method and equipment, if any, have been examined to ensure non-infringing approach to the existing patents.

This thesis encompasses the information generated by me based on experimental work carried out in the Institute. I assure and hold full responsibility for its genuineness.

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The work described in this thesis entitled "Quality by Design Approach: Role in pharmaceutical industry" has been carried out by Supreet under my supervision. I certify that this is her bonafide work. The work described is original and has not been submitted for any degree to this or any other university.

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During the above period of project work, she was committed to the assignment given to her and showed keen desire to learn and perform the task assigned methodically with initiative.

We wish her all the best for her future endeavors.

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DEDICATED TO…..

MY FAMILY

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ABSTRACT

The represented study was conducted to understand the concept of Quality by Design (QbD) and its implementation in pharmaceutical industry. QbD is an upcoming approach in pharmaceutical industries and its core objective is to design quality into the process and product rather than try to check quality of the product at the end of production. USFDA adopted the quality by design concept in 2004. QbD is based on the ICH guidelines Pharmaceutical development (Q8), Quality Risk Management (Q9) and Pharmaceutical Quality System (Q10). Information related to Quality by design is submitted in the Module 3 of CTD in pharmaceutical development section 3.2.P.2. QbD offers various advantages over the traditional system of end product testing by providing better design of product by utilizing design space which offers fewer problems in manufacturing, less time in regulatory review and approval, improves interaction with FDA by dealing on scientific level, and facilitates GMP inspection and CMC review by the regulatory bodies. From the year 2013 onwards, FDA had made it compulsory to incorporate this concept while submitting any NDA or ANDA to FDA in CDER (for human and veterinary) and CBER (for biological). In International Forum Process Analytical Chemistry (IFPAC) meeting, Dr. Daniel Peng reported that there was a gradual increment in generic industries who had filed ANDA, with the adoption of QbD principles, form 24.6% to 82.9% from June 2012 to January 2013 respectively. Astra Zeneca Pharmaceuticals, Daichii Sankyo, Merck Sharp and Dohme etc. are some of the multinational companies which are investing million and billion dollars to scientifically understand and implement QbD approach for various pharmaceutical formulations. These companies had recently filed NDAs for certain drug products who's CMC have been approved by FDA's CMC review team. Some case studies, which describe the implementation and importance of QbD approach in pharmaceutical industry, have also been described in this work.

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LIST OF ABBREVIATIONS

Abbreviation	Description
%	Percentage
ºC	Degree Celsius
>	Greater than
<	Less than
µm	Micrometer
mg	Microgram
ml	Milliliter
g	Gram
mEq/Lt	Milliequivalent per litre
ng/ml	Nanogram per millilitre
min	Minute
w/w	Weight/ Weight
ppb	Parts per billion
pH	Potency of Hydrogen
N	Number
S.No.	Serial Number
ANDA	Abbreviated New Drug Application
API	Active Pharmaceutical Ingredient
BCS	Biopharmaceutical Classification System
BBD	Box- Behnken Design
CCD	Central Composite Design
CCS	Croscarmellose Sodium
CLL	Chronic Lymphocytic Leukemia
cGMP	Current Good Manufacturing Process
CMA	Critical Material Attribute
CMC	Chemistry, Manufacturing and Controls
CPP	Critical Process Parameter

CQA	Critical Quality Attributes
CTD	Common Technical Document
DP	Drug Product
DT	Disintegration Time
D-OD	D-Optimal Design
DoE	Design of Experiments
EMEA	European Medicines Agency
FDA	Food and Drug Administration
FD	Factorial Design
FFD	Fractional Factorial Design
FMEA	Failure Mode Effects Analysis
FMECA	Failure Mode, Effects and Criticality Analysis (FMECA)
FTA	Fault Tree Analysis
GMP	Good Manufacturing Practices
HACCP	Hazard Analysis and Critical Control Points
HAZOP	Hazard Operability Analysis
HLB	Hydrophilic Lipophilic Balance
HPMC	Hydroxypropylmethyl Cellulose
HPLC	High Performance Liquid Chromatography
HSWG	High Shear Wet Granulation
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IFPAC	International Forum Process Analytical Chemistry
ISPE	International Society of Pharmaceutical Engineers
MCC	Microcrystalline Cellulose
NDA	New Drug Application
OFAT	One Factor At Time
PAI	Pre-Approval Inspection
PAT	Process Analytical Technology
PAS	Prior Approval Supplement
PD	Peritoneal Dialysis

PHA	Preliminary Hazard Analysis
PLGA	Poly(lactic-co-glycolic acid**)**
POV	Preoperational Visit
PVC	Polyvinyl Chloride
PVDC	Polyvinyldiene Chloride
PQLI	Product Quality Lifecycle Implementation
PQS	Pharmaceutical Quality System
QbD	Quality by Design
QOS	Quality Overall Summary
QRM	Quality Risk Management
QTPP	Quality Target Product Profile
RH	Relative Humidity
RLD	Reference Listed Drug
ROW	Rest of World
SSG	Sodium Starch Glycollate
TgD	Taguchi Design
TPP	Target Product Profile
TPQP	Target Product Quality Profile
US	United States
USP	United State Pharmacopoeia
USFDA	United State Food and Drug Administration

CHAPTER1

INTRODUCTION

CHAPTER 1

INTRODUCTION

Quality of pharmaceutical products has been a major concern since many years. The concept of quality system came in to picture after the disaster with the Sulfathiazole tablets tainted with sedative phenobarbital which occurred in 1941 which caused approximately 300 deaths. This incident lead to the inception of Good Manufacturing Practices (GMP) which established the quality system in pharmaceutical industry in US.[1] For safeguarding health quality products are needed which ensures that the drug product is free from any filthy material and consistently delivers the product of predefined specifications. Before discussing the quality by design concept we need to understand "Quality". Quality means that product is as per the needs of the customer and at the same time free from defects. The concept of quality is to ensure consumer satisfaction.[2] Now a days, regulatory agencies are putting emphasis on Quality by Design (QbD) concept to be implemented for the development of pharmaceuticals. QbD concept was introduced by Dr. Joseph M. Juran in 1992 who was a famous management consultant. United States Food and Drug Administration (USFDA) adopted the QbD concept in 2004.[3] As per the theory of M. Juran quality can only be developed into the product by assuring the predefining product specifications but not by subjecting the product to quality tests to ensure the product quality.[4] The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) issued guidelines for QbD i.e. Q8 for pharmaceutical development, Q9 for Quality Risk Management (QRM) & Q10 for Pharmaceutical Quality System (PQS).[5,6] According to the Q8 (R2) guidelines issued by the ICH, QbD is defined 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.[7] As per these guidelines product is developed according to its predefined quality, safety and efficacy.

1.1 Elements of QbD

QbD is the key for successful incorporation of quality in the pharmaceutical products. There are various essential elements of QbD which plays important role in achieving a quality product**.**

1.1.1 Quality Target Product Profile (QTPP): It is defined as the quality characteristics which are included in the product to ensure the product quality, safety and efficacy.[4] QTPP include detailed information on route of administration, dosage form, dosage strength, container closure system, therapeutic moiety release or delivery[7], potency, bioavailability, stability, shelf life and pharmacokinetics of the drug product.[8] Development strategy is revised from time to time based on the new information obtained during the development process of pharmaceuticals in QTPP.[4] It is also known as Target Product Profile (TPP).[8] QTPP is also well-known as Pharmaceutical Target Product Profile as per International Society of Pharmaceutical Engineers (ISPE).[9]

1.1.2 Critical Quality Attributes: During the manufacturing of pharmaceuticals various unit operations are incorporated to get the quality product. Unit process is a combination of different unit operations like mixing, milling, granulation, compression, coating etc.[5,10] According to ISPE Product Quality Lifecycle Implementation (PQLI) Critical Quality Attributes (CQAs) are defined as "physical, chemical, biological or microbiological properties or characteristics that need to be controlled (directly or indirectly) to ensure product quality." Some describe CQAs as an element of QTPP e.g. dissolution while other considers CQAs as a mechanistic factor e.g. particle size and hardness. So CQA is a result of bilateral combination.[11] As per ICH Q8(R2) "A CQA is a physical, chemical, biological or microbiological property that should be within the prescribed limits to ensure the product quality, safety and efficacy."[8] Various Critical Process Parameters (CPPs) and CQAs are given in Table 1.1. CPPs which affect the quality of the pharmaceuticals include the type of equipments used, operating conditions i.e. temperature, time, pressure, speed etc. and environmental conditions such as humidity etc. The quality of the finished product depends on the process parameters, raw materials used and the excipients incorporated.[5,10] Prior knowledge of the product is also used for evaluating quality attributes like literature knowledge, manufacturing experience, stability data, raw material testing data.[12]

Table 1.1: Various unit operations, CPPs and CQAs in tableting[14,24]

S.No.	Unit operation	CPPs	CQAs
1	Roll compaction	Speed of roller, Gap setting, Roll pressure	Appearance, Size as well as shape of particles, Ribbon density, Strength and thickness
2	Wet granulation	Dry mix time, Impeller speed, Spray nozzle type, Binder addition rate, Binder fluid temperature, Binder additional rate and time, Bowel temperature	Flow characteristics, Moisture content, Particle size distribution, Granule size
3	Drying	Total drying time and temperature, Inlet air flow, Product temperature, Shaking interval, Impeller speed	Flow characteristics, Moisture content, Residual solvents, Granule size and distribution
4	Milling	Feeding rate, Speed, Screen size and type	Particle size and shape, Flow properties, Bulk density
5	Mixing	Addition speed, Mixer load level, Time of rotation and speed of rotation	Flow properties, Moisture content, Particle size distribution, Bulk density
6	Compression	Feeder speed, Design of hopper, Tablet weight and thickness, Punch penetration depth, Roller type, Depth of fill	Weight variation, Hardness, Friability, Assay, Dissolution, Disintegration
7	Coating	Spray nozzle, Spray rate, Pan rotation speed, Gun location, Coating time	Appearance, % weight gain, Film thickness, Color uniformity, Hardness

CQAs are optimized to the maximum extent so as to get the quality product via time to time evaluation of drug product. There are some Critical Material Attributes (CMA) like particle size and hardness that are independent of each other but they affect the overall quality of the product.[11] For example, in case of solid dosage forms like tablets, hardness and dissolution depends on the polymers used and the particle size distribution within the tablet. Similarly, in case of suspension, dissolution depends directly on the suspended drug particle size.[4] COAs for different delivery systems vary, for example adhesion characteristics for sustained release transdermal patches, sterility for parenterals.[7] For this reason to achieve quality product all the CQAs are controlled within their safe limits to ensure the quality, safety and efficacy of the dosage form.[8]

1.1.3 Quality Risk Management (QRM): As per ICH Q9 guidelines, Quality Risk Management (QRM) is defined as "an efficient approach used to assess, communicate, control and review of risks associated with the drug product quality throughout the life of the product.[14] Principles of risk management are not only followed in pharmaceutical field but also in private and government sectors of business. QRM is considered as a valuable system which analyzes the product quality associated risks. It is important to identify the risks associated with the process parameters prior to the initiation of the drug development process.

Quality Risk Management principles

Risk associated to the quality of the product or process is assessed on the basis of scientific knowledge and then linked to patient safety.[14,16]

Basic components of QRM

1) Risk assessment: Evaluation of all the risk factors, which influence the quality of the product in a process, is imperative to improve the overall performance, quality, safety and efficacy of the product.[14,15,16,17] Following questions are often helpful in risk assessment:
   - What might go wrong?
   - What is the probability of occurrence of that wrong?
   - What is the severity of that wrong?

a) Quality risk identification: Information obtained from historical data, theoretical analysis, informed opinions are used to identify the risk or harm. It answers the question "What might go wrong?"
b) Quality risk analysis: The factors which are identified in earlier step are analyzed to determine how much risk is associated with the identified factor?
c) Quality risk evaluation: In this, the comparison of risks which are identified and the risks which are analyzed are done with the already established criteria. There are various evaluation tools which are used for the easy evaluation of all the parameters.
2) Quality risk control: Here, the risk factors which are identified are further reduced to the safe level so that they pose minimum harm or error in the process. The effort required to control the risk depends upon the importance of that risk in the process. It mainly highlights the following questions:
   - Is the risk in acceptable limits?
   - What are the efforts required to bring the risk to satisfactory level?
a) Quality risk reduction: This mainly concentrates on avoiding quality risk when the risk associated exceeds from its specified acceptance limit. It includes:
   - Actions which are taken to minimize the chances of rate of harm.
   - Actions which are taken to minimize the severity of rate of that harm.

   With the implementation of risk reduction, chances are that new risks may start occurring in the system. So, it is advisable to recheck the risk assessment after implementation of risk reduction to identify the other possible risks.
b) Quality risk acceptance: Quality risk acceptance is the decision taken to accept the risk. Best quality risk management practices sometimes do nothing to eliminate the risk. So appropriate quality risk management approach is used to minimize the quality risk to predefined acceptable limits. The entire process of QRM is discussed in Figure 1.1.

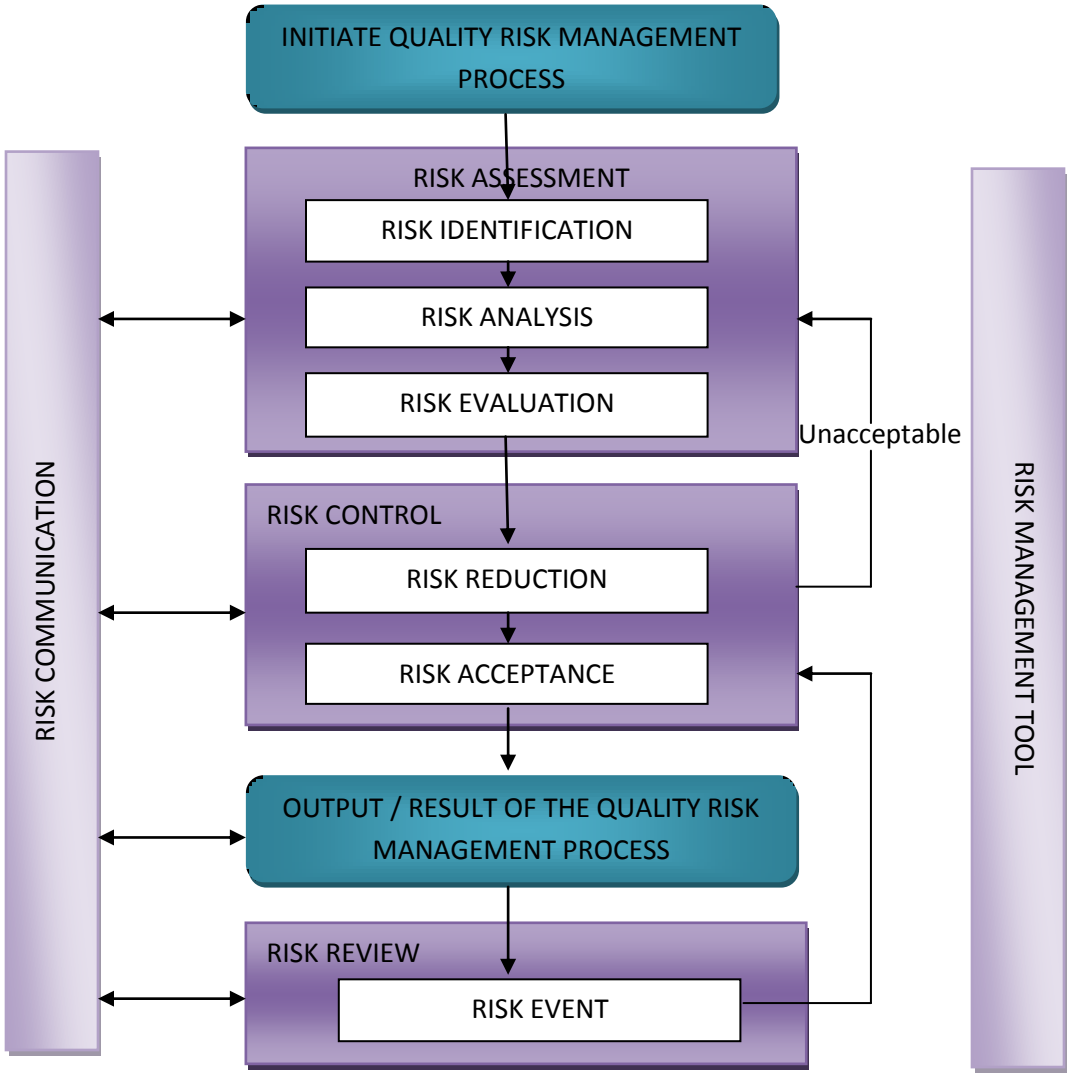

Figure 1.1: Quality Risk Management Process [17,18]

3) Quality risk communication: It involves the discussion of the associated risks and its management with the decision makers. Communication might happen between regulators and industry, industry and patients and inter disciplinary communication within the company. Communication of each and every risk, associated with the process is mandatory for its better understanding, among the individuals and different disciplines. Communication basically include discussion of nature, form, severity, probability, management or treatment of the risks identified and evaluated.

4) Quality risk review: It includes the review of the outcomes of risk management process to acquire more knowledge for a better future prospective and to minimize the errors which might occur with the passage of time during the process.

Methods of QRM

Once the harmful risks affecting the quality of the process have been identified, it may be controlled. Given below are some methods which are used for the QRM:

1) Basic risk management facilitation methods
2) Failure Mode Effects Analysis (FMEA)
3) Failure Mode, Effects and Criticality Analysis (FMECA)
4) Fault Tree Analysis (FTA)
5) Hazard Analysis and Critical Control Points (HACCP)
6) Hazard Operability Analysis (HAZOP)
7) Preliminary Hazard Analysis (PHA)
8) Risk ranking and filtering
9) Supporting statistical tools[14,16,17]

1.1.4 Design space: As per ICH, Q8 design space is defined as "the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide the assurance of quality."[7] If design space for the process or product is well established then operating within the design space will produce predefined quality products. As per the definition of the CPPs, process inputs and CQAs must be combined together to get a better result product with the implementation of design space. Pharmaceutical products with excellent results can be produced by targeting all the CPPs with in the design space.[19] CQAs are the physical, chemical, biological and microbiological properties of the drug substances which must be monitored from time to time and checked against a reference standard for the estimation of their acceptance limit.[20] As per ICH, CPPs are defined as "A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality."[7] Examples of CPPs include temperature, humidity, and fluid pressure inside pumps.

1.1.5 Quality Control Strategy: It includes our ideas, plans and strategies which are adopted to control the quality. As per ICH Q8(R1) guidelines control strategy is defined as "a planned set of controls, derived from current product and process understanding that assures product quality."[21] It is mainly concerned with the attributes and parameters of drug substance, drug product components, equipment operating conditions, in-process controls and finished product qualifications etc.[9,21,22] Quality control strategy includes following essentials:

1) Procedural controls
2) In-process controls
3) Process monitoring
4) Lot release testing
5) Stability testing[11, 23]

Risk assessment plays essential role in the establishment of strategy to control all the parameters or the attributes that causes risk to the quality. ANDA sponsor utilizes control strategy to ensure that quality products are consistently provided as they scale up their batch to the commercial level.[11,23] Control strategy to retain the quality of the product is adopted during the whole process starting from the raw material specification determination to the drug product manufacturing, packaging and distribution.[9]

There are basically two approaches in ICH Q8(R) for control strategy:[9]

1) Minimal control strategy approach: In this approach, the quality of the drug products is confirmed by in-process and end product testing.
2) Enhanced control strategy approach: In this approach, risk based control strategy of product and process is adopted for assuring the quality of drug product and by adopting real time release strategy or reducing the end product testing.

Quality of the drug product is ensured by testing of drug substances and the excipients prior to their utilization in the manufacturing of the drug product to ensure that they meet the standards specified in the United States Pharmacopoeia (USP). Manufacturer also do in-process testing (i.e. tablet hardness testing) besides testing the specification limits of the drug substances. The manufacturing process also needs to be strictly controlled. If there is any

deviation made in the operating parameters by the manufacturer then they need to file a supplement of changes with the FDA. As per the current quality control strategy the combination of fixed manufacturing steps and extensive testing is very critical. This current system needs to be strictly monitored because the manufacturers do not understand the role of drug substance, excipients and rigidity of process parameters in the quality of the drug product and any changes made in the process parameters are not communicated to the FDA's Chemistry, Manufacturing and Controls (CMC) reviewers.[6,23]

1.1.6 Continuous improvement: The main focus of QbD is to develop quality within a product and to make continuous improvement within a process by minimizing chances of variability. Continuous improvement focuses on improving efficiency of product as well as of process by optimizing the latter. PQS is essential for the continuous improvement of product or process as it helps in identifying the possible causes of variation, process improvements and innovation enhancement. Examples of continuous improvement include new equipment of same design but having more efficiency, changes made in a process, simplifying documentation work, changing design space, removing unit operation etc.[9]

1.2 Traditional approach &QbD approach

There are two ways for developing biopharmaceutical products as well as conventional drugs which are commonly used i.e. traditional approach or "One Factor at a Time" (OFAT) and QbD approach. Traditional approach is one factor approach, where only one factor is studied against the response of our interest and remaining factors are kept constant. Next factor is considered only when the effect of first factor on the selected response is determined. This process of studying the effect of factor against response is continued until a satisfactory result is not produced. For this reason it is named as One Factor at a Time i.e. OFAT. When all the factors are combined together and checked against one or more factors there are chances that they interact with each other and results may vary. For this reason, it produces just satisfactory results.[24] In traditional pharmaceutical development approach, the quality of products is confirmed by testing raw materials, drug substance manufacturing, in-process material testing and finished product testing. The testing of finished product is carried out to conform that its specifications match with the specification limits prescribed by the USP or by the FDA. If it is not upto the prescribed specifications then it is rejected. In this approach

we cannot identify the cause for the error occurring in the product, so it is regarded as risky and costly approach which sometimes leads to product recall.[25] There are several drawbacks of OFAT over systematic approach which are as follows:[26]

1) Several experiments are done to study the effect of each factor in a process
2) Futile when all variables change simultaneously
3) Prone to misinterpretation of results
4) Time consuming and costly approach
5) Inapt to reveal interactions
6) Unsuitable to plug errors
7) Produces just satisfactory results

In the 1940s during the World War II systematic approach came in origin with its implementation in the chemical industry. Later on, it started emerging in other industries too i.e. semiconductor, oil refining, automobile industries etc. so as to enhance the quality of the products being manufactured by them.[26] But the systematic approach was realized in the pharmaceutical development with the initiative taken in 2002 with "Pharmaceuticals cGMPs for the 21st century: A risk based approach" and USFDA adopted and implemented this approach in 2004 for providing better regulations for the pharmaceutical products and ensuring the quality of the pharmaceuticals.[27] QbD is a scientific and risk based approach in which multiple variables are studied at a time using a design space. In this, various process parameters and quality attributes are controlled to maintain the quality of the products.[25]Difference between traditional and systematic QbD approach is discussed in Table 1.2.

Table 1.2: Difference between Minimal/ traditional approach and Quality by design approach[6,7]

Aspect	Traditional approach	QbD approach
Overall pharmaceutical development	Developmental research often conducted on one variable at a time	Multivariate experiments to understand product and process
Manufacturing process	Fixed	Adjustable within the design space
Broad concept	Quality decisions are not made on scientific and risk evaluation. Focuses on completing filing commitments	Filing commitments and decisions are based on scientific and risk management by adopting design space
Quality control strategies	Quality of drug product is controlled by intermediate and end product testing	Quality of drug product is guaranteed by risk based control strategy
Regulatory focus	Changes made requires prior approval, lengthy process and results are not known at all	Regulatory check adjusted to level of process understanding and further upgrading of product is allowed within the design space

1.3 QbD implementation

It is a very challenging task to implement a QbD concept in the development of the formulations. There are several tools which are available for the better and effective implementation of the QbD i.e. Design of Experiments (DoE), Process Analytical Technology (PAT) and Risk Management Methodology.[10,28] Joseph M. Juran described a "quality planning roadmap" for the better implementation of QbD. He described nine steps for the effective quality planning, which are as follows:[28]

1) Customer identification
2) Finding the needs of the customers
3) Translating needs of the customer into company language

4) Product designed to satisfy customers need
5) Optimizing the product as to satisfy both the customer and company's needs
6) Development of an effective process for the manufacturing of a product
7) Process optimization for achievement of the product with the better quality
8) Controlling the operating parameters to develop consistently better quality products
9) Transferring the process to operations

1.3.1 Design of Experiments (DoE)

While conducting any experiment some changes are done in the process to check its effect on the response by analyzing the data obtained. This helps in achieving objectives of the experiment effectively. So, Design of Experiment (DoE) or Experimental Design is laying out of detailed experimental plans in advance to conduct the experiment.[29] Statistical design of experiment is a useful technique to obtain association among CPPs and CQAs. DoE is adopted for development and optimization of manufacturing processes. It is adopted in various industries i.e. electronics, mechanical and pharmaceutical industries for the synthesis of various compounds and for the optimization of analytical instruments.

Advantages of DoE:

1) Developing new products and processes
2) Optimization of quality and performance of a product
3) Optimization of an existing product
4) Minimization production cost
5) Robustness testing of products and processes
6) Obtaining maximum information by performing minimum number of experiments
7) Easily analysis of interaction between the process parameters
8) Easily trace and rectify problems

Problems solved by DoE:

DoE approach is used to study the effect of various factors on a process or system at a single time which is not possible by OFAT.[30]

Various experimental designs that are used in pharmaceutical product as well as process developments are:[26,31]

1) Factorial Design
2) Fractional Factorial Design
3) Box- Behnken Design
4) Optimal Design
5) Central Composite Design
6) Taguchi Design

Choice of DoE:

It is very important to choose the experimental design which suits our study, nature of risks, factors associated, interactions to be studied (e.g. four, six or nine factors) and the most important available resources (e.g. time, material, cost etc.). In addition to this, the knowledge which is previously obtained from the literature and form the experimentation is also helpful in selecting the experimental design.

1.3.2 Process Analytical Technology (PAT)

It ensures the voluntary development, execution of innovative pharmaceutical development, manufacturing and quality assurance. It also ensures the safety of patients as well as enhances the profitability of manufacturing industries by timely measurement of CQA of raw materials and processes which are key elements to enhance the quality of product. The term "analytical" in "PAT" means a chemical, physical, microbiological and risk analysis of each component used in the manufacturing process. [32,33]

The main motive behind development of PAT is to design well understood processes that will eventually lead to the achievement of predefined quality at the end of the manufacturing process i.e. quality should be built in product by designing and it should not be obtained by testing the product at the end of the manufacturing process. Process seems to be well understood when:

- Sources of variability are well recognized in advance
- Variation is controlled in the procedure
- Product quality attributes are identified properly

PAT includes the thorough understanding of:

- Therapeutic effect, patient population, administrative route, pharmacological, toxicological and pharmacokinetic parameters of the medicine
- Chemical, physical and biopharmaceutical characteristic of medicine
- Selection of product components and packaging as per the drug to be used
- Design of manufacturing process include proper implementation of the principles of engineering and material sciences to ensure the reproducible product quality[32,33]

PAT structure has two components:

- Scientific principles and tools supporting innovation
- A strategy for regulatory execution that contains innovation

Benefits obtained from PAT framework:

- Reduction in production cycle times by adopting in-line, on-line or at-line measurements and controls
- Prevents rejects and reprocessing
- Improves efficiency and manages variability
- Efficient energy and material use [32,33]

1.4 Software's for QbD

For the proper implementation of QbD various mathematical and statistical tools are required. Computer software's which are available for QbD studies for DoE optimization include:[31]

1) Design-Expert
2) MODDE
3) Unscrambler
4) JMP
5) Statistica
6) Minitab[28]

1.5 Benefits of QbD

QbD offers various advantages:

1) Provides better design of product by utilizing design space which offers less problems in manufacturing
2) Provides better consistency
3) Decision are made on scientific knowledge and not on empirical information
4) Provides better coordination during review and inspection process
5) Improves information on regulatory submission
6) Reduces regulatory review timing and provides quick approval
7) Reduces overall cost of manufacturing
8) Allows for better and effective incorporation of technologies for product development without regulatory scrutiny[36,37]
9) Continuous improvement in products and manufacturing process
10) Improves interaction with FDA by dealing on a scientific level[29]

1.6 Challenges to QbD

Not all companies have adopted QbD inspite of the recommendations of FDA, despite of the fact that application will provide operational and financial benefits to industries by reducing the chances of batch rejection. The possible barriers to the QbD adoption are as follows:

1) Lack of understanding of QbD and resources too
2) Lack of adaptability for this new concept
3) Organizational resistance to do changes in the manufacturing process
4) Industries are of the view that QbD slows down the time for approval of the application due to incorporation of unnecessary information
5) Effective coordination and cooperation among process development, manufacturing and quality control departments are required for the better execution of QbD
6) Organizations are saying that our product is already under control, not need to do changes
7) Benefits of QbD are not well known
8) Pharmaceutical industries are putting more emphasis on testing the quality of the product at the end instead of scientific and more effective understanding of process.[12,36]

1.7 QbD approach for development of drug product

In literature, the concept of QbD was adopted for variety of drugs, to know its effect on the final drug product. List of these drugs are given below in Table 1.3.[31]

Table 1.3: QbD approach utilized for variety of drugs[31]

Drug	QTPP	CPPs	CQAs	DoE
Nimesulide	Liposomes	Amount of phospholipid, cholesterol	Percent entrapment, percent diffused, percent leakage	FD
Tramadol	Controlled release bioadhesive tablets	Carbopol 971P and HPMC	Drug release in 16hr, bioadhesion strength, release exponent	CCD
Paclitaxel	Nanoparticles	PLGA amount, surfactant conc., homogenization rate	Particle size, zeta potential, encapsulation	BBD
Solid dispersion	Spray drying process	Temperature, concentration, flow rate	Outlet temperature, size of particles	BBD
Nanoparticles	Milling process of media	Speed of motor and pump, homogenization time	Particle size, yield	CCD
Tamoxifen	Lecithin organogels	Amount of organic phase, water and pluronic	Viscosity, gel strength, spreadability, consistency	D-OD

CHAPTER 2

LITERATURE REVIEW

CHAPTER 2

LITERATURE REVIEW

1. ***Lambert JW, (2010):*** Target Product Profile (TPP) describes the utilization of the product by the users. It include whole description of dosage form, dosage strength, route of administration, pharmacokinetics etc. of the drug product. TPP is considered important for the parenteral dosage forms due to variety of end product users (i.e. patients, physicians, pharmacists etc.) and requirements specific to the sterile products.
2. ***Nagar M, et al, (2010):*** Implementation of QbD principles during product development help in continual improvement in product lifecycle. It is for this reason is considered as a most convenient approach for developing quality product. It is the best approach which increases process as well as product understanding which will be helpful throughout the product lifecycle. There is a reduction in product recall chances as we acquire knowledge regarding product and process for developing the formulation. QbD filling also facilitate CMC reviews and GMP inspection by regulators and thus reduces the chances of Prior Approval Supplement (PAS) submission for doing any changes in the process.
3. ***Staples AM, (2010):*** FDA had taken initiative for enhancing regulations related to pharmaceutical products manufacturing as well as quality. As a result of this effort, ICH had issued guidance on development of pharmaceutical product via ICH Q8 guidelines on QbD concept. QbD lead to better-understanding of products and manufacturing processes that will be subjected to less variability in quality. FDA hoped that QbD incorporation in manufacturing of pharmaceuticals would enhance product as well as process understanding and also improve regulatory flexibility requiring no regulatory submission.
4. ***Anuj G, et al, (2012):*** QbD is a systematic as well as modern approach in pharmaceutical quality system. Its main or major focus is to develop formulation to achieve the predefined quality of products. Important QbD elements are TPQP, CQAs, CPPs and design space.
5. ***Nadpara NP, et al, (2012):*** QbD is the most upcoming and modern approach for developing pharmaceuticals with quality. It offers many advantages over the traditional approach and provides process as well as product understanding which is useful for pharmaceuticals development as well as for their continual improvement. Quality should

be created in the product rather than testing the product for checking its quality at the end. It includes various elements i.e. QTPP, CQAs, CPPs which are described in detail in Pharmaceutical development (Q8); QRM (Q9) and PQS (Q10) guidelines.

6. ***Kamble NR, et al, (2013):*** QbD is getting importance in pharmaceutical industries and many companies are adopting this concept for the development of the formulations. CPPs and CMAs result in the progress of design space. Any changes related to formulations which are done within the design space need no regulatory submission. This concept focuses on QRM which is defined in ICH Q9 guideline.
7. ***Patel H, et al, (2013):*** As of now QbD is considered as a vital and modern approach for developing pharmaceuticals of the best quality. For the generic manufacturers, developing a product by using QbD principles is very challenging because neither are they aware of terminologies which are used in QbD nor how to implement QbD in pharmaceuticals. QbD ensures drug development with increased efficacy provides support to regulatory body during reviewing and also ensures improvement in drug product throughout the lifecycle of drug product. QbD approach is also helpful in development of pharmaceutical industry. For successful and fruitful implementation of QbD, cooperation among company employees is required so that they can help each other in achieving their targets.
8. ***Siddiqua SA, et al, (2013):*** QbD besides being considered as the best approach for developing quality in pharmaceuticals is also the most challenging approach for pharmaceutical industries to implement it without causing any variation in the fixed parameters. For developing a quality product it is significant to have idea regarding QTPP and CQA of drug substance which are going to influence drug product quality, CPP which are going to affect CQA if any variation is done in it. QbD is the only approach in the present time which provides quality products by maintaining stringent quality standards.
9. ***Chaudhari AR, et al, (2014):*** QbD has been regarded as holistic approach for the quality of pharmaceutical products. One of the major challenges to pharmaceutical industry is the understanding and execution of quality by design concept. QbD mainly focuses on determining product performance profile which includes TPP, CQA, CMA, CPPs.

10. ***Jain S, (2014):*** Pharmaceutical industries are very much worried about the quality, safety and efficacy of the pharmaceutical products due to increased regulatory burden, increased product recalls. Regulatory bodies are focusing on science based approach i.e. QbD concept for the thorough understanding of the process parameters which are lacking in traditional approach i.e. quality by testing approach. Pharmaceutical industries are mainly focusing on better implementation and understanding of QbD principles.
11. ***Kamboj S, Chopra S, (2015):*** USFDA introduced QbD in 2004, its main motive is to build quality within the product rather than checking the product during end time release testing. ICH had issued Q8 guidelines in 2005 i.e. for pharmaceutical development describing the concept of design space. Pharmaceutical companies are adopting QbD in various NDAs and ANDAs.

CHAPTER 3

OBJECTIVES OF THE STUDY

CHAPTER 3

OBJECTIVES OF THE STUDY

3.1 To obtain understanding of the QbD approach.

3.2 To provide an overview and understanding of various elements of QbD approach.

3.3. To review the application and significance of QbD approach in pharmaceutical industries.

3.4 To review the data to be submitted in Pharmaceutical development section, having QbD approach in Module 3 of dossier.

3.5 To review data on NDA, developed by QbD approach, submitted/approved by FDA.

3.6 To understand the role of QbD approach in pharmaceutical industry.

CHAPTER 4

WORK METHODOLOGY

CHAPTER 4

WORK METHODOLOGY

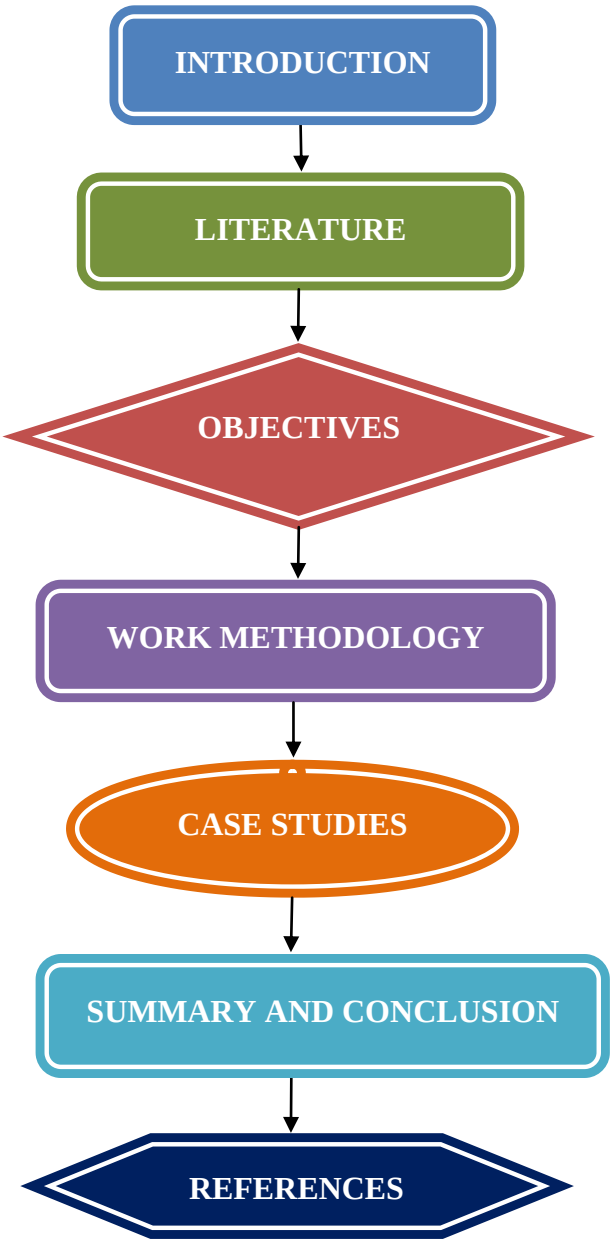

Figure 4.1: Plan of work

In the current study major part of the data was collected by:

4.1 Exhaustive literature search from various national and international journals, market research reports and news articles. Search for latest regulatory guidelines related to QbD was also done. Some case studies reflecting the use of QbD in pharmaceutical industries were also obtained from journals and web links.

4.2 Internet using web links: Literature was collected from several web links e.g. pubfacts.com, pharmtech.com, in-pharmatechnologist.com, pharmoutsourcing.com, fda.gov, pharmaqbd.com etc.

CHAPTER 5

CASE STUDIES

CHAPTER 5

CASE STUDIES

5.1 Case study I: Development of dispersible tablets of Diclofenac

FDA made it compulsory to initiate QbD for building quality in pharmaceutical products rather than checking the product quality at the end of the manufacturing process. While scaling up from research and development to production scale several changes occurred with respect to CQAs, CPPs etc. resulting in product deviation from the specifications. This increases the chances of batch rejection. This could be attributed to the lack of product as well as process understanding that led to the wastage of resources and economy. Even post approval changes also need regulatory approval prior to their application in commercial production. QbD ensures quality of the product throughout the manufacturing process.

Dispersible tablets are uncoated or film coated tablets that can be dispersed in water before administration giving a homogeneous dispersion. These tablets usually disintegrate within three minutes after putting in water or in any aqueous solution.

These tablets generally offer various advantages over the conventional dosage forms:

- Easy to administer especially for pediatric and geriatric patients
- Fast disintegration
- Fast absorption

To fasten the disintegration of the dispersible tablets compression force should be less as compare to other conventional dosage forms which directly influences the hardness of tablet.

For establishing the design space QTPP, CPPs, CQAs should be known in advance prior to the manufacturing. QTPP depends upon the nature of the drug product. In Diclofenac dispersible tablets, QTPP are mainly related to the pharmacological aspects of the drug i.e. indications, side effects, route of administration, dosage form, dosage strength, pharmacokinetics etc. For the generic drug products, QTPP are generally obtained from the innovators product. QTPP provides summary of quality characteristics of drug product that should be achieved to obtain predefined attributes of product. Prior to the start of drug product manufacturing, risk assessment is done to know possible interactions between

excipients, drug and several unit operations utilized for manufacturing. CQAs are determined from QTPP, prior knowledge of product and process.

Observations:

Study 1: Impact of packaging material on stability of Diclofenac drug product

Literature on the Diclofenac reveals that the drug is sensitive to moisture. Therefore, packaging material should be selected very carefully so that the drug will not absorb moisture while storing in warehouse or during transportation. Stability study carried on drug reflected that the drug should be handled and processed below 60% relative humidity (RH) as above this value drug absorbs moisture from the environment as it is reflected in Figure 5.1.

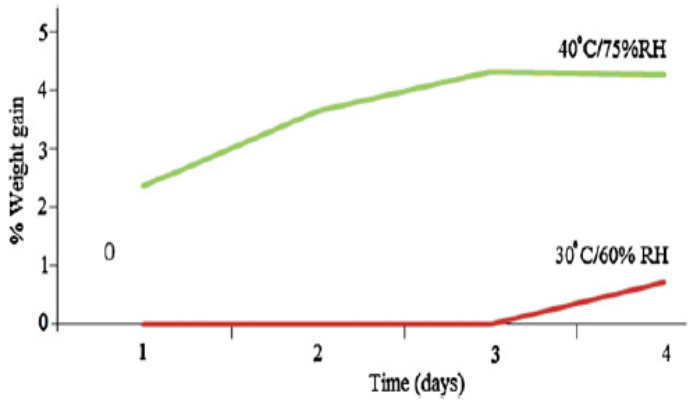

Figure 5.1: Percent weight gain in drug product when exposed to different conditions[38]

For proper selection of the packaging material study was conducted. Firstly tablets were prepared from following:

- Microcrystalline Cellulose (MCC) 220mg/tablet
- Sodium Starch Glycollate (SSG) : Croscarmellose Sodium (CCS) 1:2.2
- Magnesium stearate 0.5%

Tablets were packed in different blister packs made of:

- Polyvinylchloride (PVC)
- Polyvinylchloride/ Polyvinyldiene Chloride (PVC/PVDC)

These packs were then stored at 40ºC/ 75%RH for 3 months and then analyzed by HPLC and it was observed (Figure 5.2) that the packaging material made from PVC/PVDC contained % total impurity significantly lesser than 0.05% in formulation compared to when it was made

from PVC alone (0.23%). PVDC is normally added in the composition of packaging material to enhance the moisture barrier properties of PVC alone.

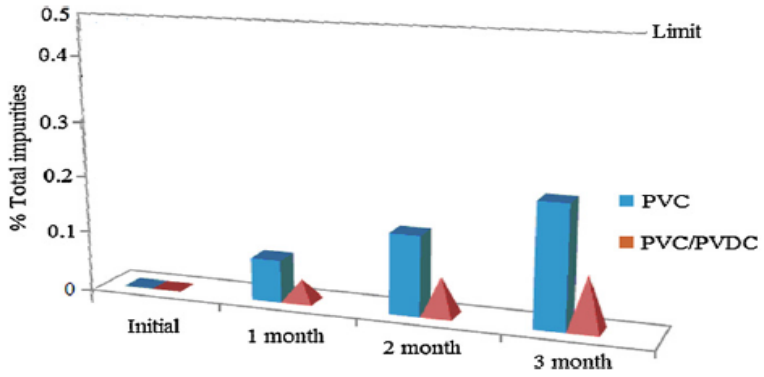

Figure 5.2: Packaging material effect on drug product degradation[38]

Study 2: Effect of lubricants concentration on Disintegration Time (DT) of tablets

Magnesium stearate is a hydrophobic lubricant used in tablet formulations and also commonly used to increase the DT. Magnesium stearate is added in different concentrations i.e. 0.5%, 1.0% and 1.5% in tablet and analyzed for its effect on DT and dissolution rate.

It was observed that there was no significant effect (p>0.05%) of magnesium stearate concentration on DT of tablet as shown in Figure 5.3.

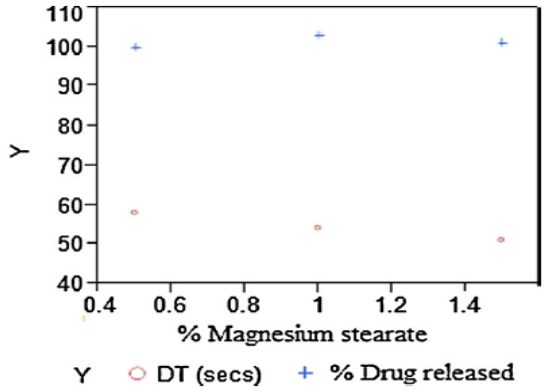

Figure 5.3: Effect of concentration of magnesium stearate on disintegration time of tablets[38]

Conclusion:

For improving quality of dispersible tablet, QbD approach was utilized which include quality management program and continuous improvement program. For obtaining a quality product offering minimum errors, effect of packaging material used for storing the drug and lubricant

concentration used in formulating the dispersible tablet was studied for controlling all the CQAs associated with the drug substance.[38]

5.2 Case study II: Effect of Poloxamer on the dissolution rate of tablets

QbD approach needs predefining of QTPP for product, processing parameters and CQA related to finished drug product prior to establishing the design space. Risk assessment was done to identify the risks associated with the formulation of immediate release tablets and its manufacturing. From the risk assessment it was observed that High Shear Wet Granulation (HSWG) is the most critical unit operation in controlling CQA of drug products. Further, effect of poloxamer, total content of water in binder/ poloxamer solution and addition rate of binder on CQA of drug product was analyzed. Total 13 formulations were prepared to analyze the overall effect of CPPs and formulation parameters on CQA of drug product (see Table 5.1).

Table 5.1: DoE, disintegration time and dissolution profile of 13 runs[39]

DOE run number	Poloxamer 188 (%w/w)	Granulat-ing water (g)	Binder addition rate (g/min)	Tablet DT range (N=6) (min)	Timepoint, condition	Percent released at 15 min (+% change)(N=6 tablets)
1	1.5	162	58.5	10.6-12.9 4-4.7 5.5-7.0	Initial: 1 month, 40ºC: 1 month 40ºC/75% RH	50 69 (+19) 72 (+22)
2	0	147	58.5	6.2-6.6 3.7-4 5.0-5.8	Initial: 1 month, 40ºC: 1 month 40ºC/75% RH	66 69 (+3) 72(=6)
3 (center point)	3	147	58.5	11.5-13.1 5.5-6.4 8.3-10	Initial: 1 month, 40ºC: 1 month 40ºC/75% RH	43 54 (+11) 74 (+31)
4	1.5	147	48	10-11.9 3.5-4.3 7.2-8.5	Initial: 1 month, 40ºC: 1 month 40ºC/75% RH	ND ND ND
5	6	147	58.5	14.3-14.9 11.3-12 13-16	Initial: 1 month, 40ºC: 1 month 40ºC/75% RH	38 51 (+13) 46 (+8)
6 (center point)	3	147	58.5	10.2-11.1 3-3.3 8-8.5	Initial: 1 month, 40ºC: 1 month 40ºC/75% RH	ND ND ND

DOE run number	Poloxamer 188 (%w/w)	Granulat-ing water (g)	Binder addition rate (g/min)	Tablet DT range (N=6) (min)	Timepoint, condition	Percent released at 15 min (+% change)(N=6 tablets)
7	4.5	158	66	14.1-15.6 8.2-8.6 12-13.8	Initial: 1 month, 40ºC: 1 month 40ºC/75% RH	38 44 (+6) 52 (+14)
8 (center point)	3	147	58.5	ND	ND	ND
9	4.5	158	51	ND	ND	ND
10	1.5	132	58.5	ND	ND	ND
11	1.5	147	69	ND	ND	ND
12	4.5	136	66	11.3-14.9 8-9.3 10-14	Initial: 1 month, 40ºC: 1 month 40ºC/75% RH	ND ND ND
13	4.5	136	51	ND	ND	ND

ND means not done

From Table 5.1 it was observed that there was reduction in dissolution of tablet with gradual increase in surfactant concentration. Surfactant has the property to increase dissolution by enhancing hydrophilicity within the tablet and by increasing drug solubility. But in this case study, poloxamer 188 surfactant retarded the dissolution of BCS class II tablet. Reason for downfall in the dissolution was explained at the end in this case study.

Formulation:

Tablet was comprised of:

- Drug (BCS class II) 70%w/w
- Microcrystalline cellulose (Avicel PH-101) as diluent
- Poloxamer 188 as wetting agent
- Povidone K25 as binder
- Crospovidone as disintegrant
- Magnesium stearate as lubricant

In this case, the wetting behavior was dependent on the drug used, since the tablet contained approximately 70%w/w of drug of BCS class II category, having low solubility and high permeability. Poloxamer added in the binder solution helped to lower the interfacial tension between lipophilic poorly soluble drug particles by spreading over it. Poloxamer is a nonionic triblock copolymer widely used as emulsifier, wetting agent and suspension

stabilizer in oral, topical, emulsion and parenteral dosage forms. Poloxamer is freely soluble in water and having HLB value 29. Key role of Poloxamer in formulation is to enhance solubility and bioavailability of drug by improving wetting property of the drug particles.

Results observed:

Study 1: Granule size, tablet disintegration and dissolution

Figure 5.4 indicated that with increase in poloxamer concentration:

- coarse fraction increases i.e. % granules > 200µm
- fines fraction decreases i.e. % granules < 100µm
- DT of tablet increases

From Figure 5.5 it was observed that with increase in poloxamer concentration the granule size and dissolution at 15 and 30 minutes decreases.

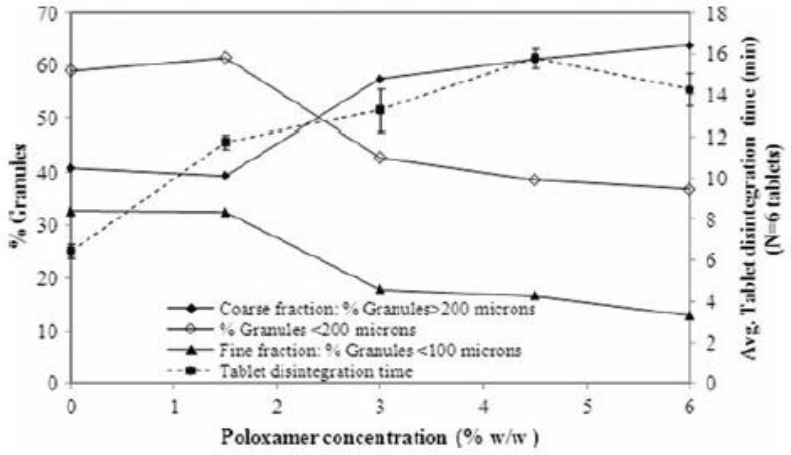

Figure 5.4: Effect of poloxamer concentration on granule size and disintegration time[39]

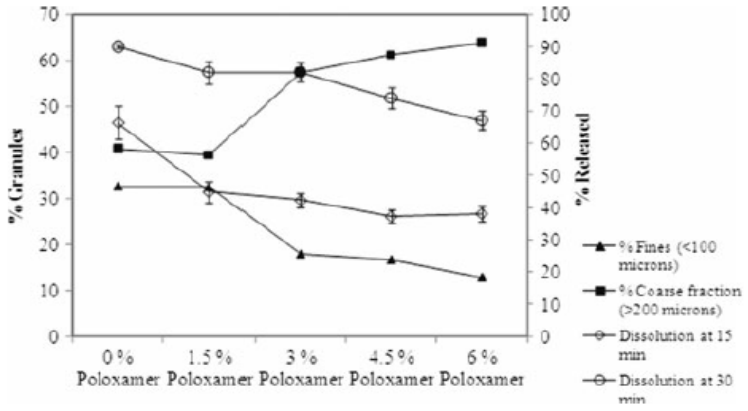

Figure 5.5: Effect of poloxamer concentration on granule size and tablet dissolution[39]

This indicated that the poloxamer concentration was affecting the granule size, disintegration as well as the dissolution of tablets.

Study 2: Accelerated stability studies effect on tablet dissolution

Each runs of DoE were exposed to accelerated stability study i.e. at 40ºC/75%RH and at 40ºC to check its effect on dissolution behavior of tablet and contrary to the initial observation that poloxamer concentration decrease dissolution of tablet it was observed that the dissolution of tablet increased when the tablets were exposed for 1 month at 40ºC in open dish and at 40ºC/75%RH as reflected in Table 5.1. This increase was observed early at 15 minutes time point.

Study 3: Effect of granules and tablet dissolution at release

It is clear from the Figure 5.6 that the dissolution and the disintegration of the tablet were mostly affected by concentration of poloxamer and lesser by water amount and binder addition rate as clearly depicted by steeper slope for poloxamer and less for the other two factors i.e. water content and binder addition rate. Thus, it was clear that to improve the dissolution and disintegration, poloxamer concentration should be properly monitored.

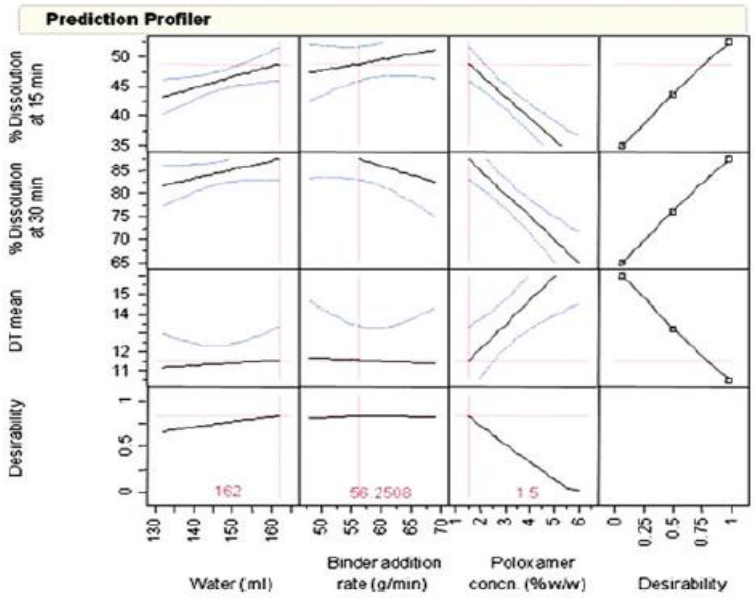

Figure 5.6: Effect of poloxamer concentration on dissolution and disintegration time observed from the slope[39]

Reason for decrease in disintegration and dissolution by increase in poloxamer concentration are:

1) Disintegrant Crospovidone increased wicking and swelling action which was the reason for enhancing the disintegration of tablet but due to increase in hydrophilicity of tablet matrix due to poloxamer, the disintegration property of Crospovidone was exhausted.
2) Poloxamer also possess binding agent property which enhances binding action of binder (in this case Povidone K25) by improving wetting of drug and excipients blend in tablet, this caused increase in particle size of the granules which then altered the dissolution of the tablet.[39,40]

5.3 Case study III: Assessment of leachable/ extractable in pharmaceutical products

QbD is the upcoming approach for developing pharmaceuticals. Developing a drug product with in the design space provides assurance of quality. In this study, QbD approach was utilized for the assessment of leachables present in the drug product stored in a packaging system.

Critical variables found in this design space are those which tend to alter the interaction between drug product and its packaging. These are as follows:

1) Drug product composition: Overall chemical characteristics of drug product may be one of the reason for leaching e.g. pH, solubility etc. Solubilizers and stabilizers incorporated in the formulation can also cause leaching but these are not included in design space. Excipients which are included in formulation, even if not impacting drug product's polarity, can be included in the defined design space.
2) Packaging system material of composition: Extent of leaching also depends upon the composition of packaging system i.e. quality and quantity of incorporated substances. So, any alteration in the material of construction of packaging system has a marked impact on the leachable contents present the system.
3) Configuration of packaging system: Surface area of contact between drug product and packaging system also causes leaching. The surface area which is in contact with drug product varies from product to product. It is observed that contact surface area is inversely proportional to fill volume (i.e. size of packaging system). So it means that

maximum contact surface area occurs with smallest fill volume which causes quickest leaching.

4) Contact conditions: It means that the time and temperature of contact between drug product and packaging system also influences leaching because these conditions alter the physiochemical properties of both the drug product and the packaging system.

There are basically two types of interactions which occur between drug product and packaging system and these are:

1) Reductive interactions: Components of drug product are moved from drug product to the packaging system.
2) Additive interactions: One or more of the components of packaging system are migrated into the drug product.

There are various packaging systems which are used for storing the drug products. These packaging systems are characterized according to their extractable profile which is detected by filling packaging unit with aqueous solution of pH 2-8. If any extractable is found in the preparation then they are tested for toxicological safety assessment. Design space is then established depending upon the toxicological implication of extractable. Such design space addresses fill volume, composition of solution, sterilization conditions and storage conditions for the drug product.

Study: Packaging system used in this case was constructed from polyolefin material. Different drug products (i.e.DP1-DP12) were made by varying their formulation and pH range, details of these are provided in Table 5.2.

Table 5.2: Different drug product formulations with varied pH[41]

Solution Code[1]	Container size (ml)	Formulation	pH range
Simulating solvents	50	pH 2, pH unadjusted, pH 9	2-8
DP1	250	10 mg/ml drug, iso-osmotic saline, acetate buffer	Not specified
DP2	250 (200)[2]	2 mg/ml drug, 0.9% saline	4-8
DP3	50	2.5 mg/ml drug, 4.6% dextrose, DL-Lactic acid	3.2-3.6
DP4	50	0.64 mg/ml drug, iso-osmotic saline, citrate buffer	3-4
DP5	100, 250 (200)[2]	2 mg/ml drug, 5% dextrose	3.5-5.5

Solution Code[1]	Container size (ml)	Formulation	pH range
DP6	100, 250 (200)[2]	2 mg/ml drug, 5% dextrose	3.5-4.6
DP7	50	5 mg/ml drug, 5% dextrose	3.8-5.8
DP8	100	0.2 mg/ml drug, 5% dextrose, DL-Lactic acid	3.4-3.8
DP9	100	0.2 mg/ml drug, 5% dextrose, L-Lactic acid	3.4-3.8
DP10	250	1 mg/ml drug, iso-osmotic saline, acetate buffer	4.9-5.1
DP11	100, 250 (200)[2]	1.25 mg/ml drug, 0.9% saline	4.0-6.5
DP12	50	50 mg/ml drug, iso-osmotic saline, acetate buffer	4.0-5.5

[1]DP means Drug Product with unnamed API

[2]250 (200) means a 200 ml underfill of a 250 ml container

Packaging units were filled with three different solutions, water, pH2 and pH8 and then subjected to terminal sterilization followed by storage at 40ºC for 6 months. This stability study condition is generally accepted as accelerated aging condition for the products. The samples were then analyzed using chromatographic method for identifying concentration of extractable substances. The drug product was also exposed to same conditions so as to analyze the concentration of the extractables present. Targeted compounds which were found given in Table 5.3.

Different extractables found in the study are:

1) CE 228 [II]: 1,8-Dioxacyclotetradecane-2,7-dione
2) Irganox degradate #2: 3,5-bis(1,1-dimethylethyl)-4-hydroxy-benzenepropanoic acid
3) Irganox degradate #3: 3,5-bis(1,1-dimethylethyl)-1-hydroxy-4-oxo-2,5-cyclohexadiene-1-propanoic acid
4) BPAT: Bisphenol A bis(2,3-dihydroxypropyl) ether
5) Octanoic acid
6) MEHP: Mono(2-ethylhexyl) phthalate

Table 5.3: Targeted extractables found in fill solution[41]

Simulating solution	**Concentration of target extractables in the fill solution (Extract), ng/ml (ppb)**											
	CE 228 (II)		Irganox degradate #2		Inganox degradate #3		BPAT		Octanoic acid		MEHP	
	TO[1]	6 mths, 40ºC	TO[1]	6 mths, 40ºC	TO[1]	6 mths, 40ºC	TO[1]	6 mths, 40ºC	TO[1]	6 mths, 40ºC	TO[1]	6 mths, 40ºC
pH 2	<100[2]	<100[2]	<100[2]	<100[2]	<100[2]	<100[2]	<100[2]	620	<100[2]	<100[2]	<100[2]	<100[2]
Water	620	130	<100[2]	<100[2]	<100[2]	<100[2]	200	410	410	260	<100[2]	<100[2]
pH 8	200	100	750	300	1300	800	120	120	1600	2200	390	500

[1]TO means samples tested after autoclave sterilization with minimal post-autoclave storage

[2]<100 means the concentration of target leachable in the drug product was less than the quantitation threshold of 100ng/ml parts per billion (ppb)

Result:

The accumulation level of targeted leachables given in Table 5.4 was generally found out to be less than or equal to 1.0 but in case of octanoic acid in DP12 target leachables concentration in drug product was found out to be more than 1.25. Further even in this DP12, the concentration of octanoic acid in drug product was found out to be less than the targeted leachables found in water.

Table 5.4: Octanoic acid accumulated as target leachable[41]

Drug product	**Container size (ml)**	**Relative concentration of the target leachable**		
		At time zero[2]	3 months, 40ºC	6 months, 40ºC
DP1	50	NMT 100[5]	NMT 100[5]	NMT 100[5]
DP2	250 (200)		NMT 100[4,5]	
DP3	50	NMT 100[5]	NMT 100[5]	NMT 100[5]
DP4	50	NMT 100[5]	NMT 100[5]	NMT 100[5]
DP5	100 250 (200)	NMT 100[5]	NMT 100[5]	NMT 100[5]
DP6	100	NMT 100[5]	NMT 100[5]	NMT 100[5]
	250 (200)	NMT 100[5]	NMT 100[5]	
DP7	50	NMT 100[5]	NT[3]	NMT 100[5]
DP8	100	NMT 100[5]	NMT 100[5]	NMT 100[5]
DP9	100	NMT 100[5]	NMT 100[5]	NMT 100[5]
DP10	250	NMT 100[5]	1.17	1.19
DP11	100	0.70	1.18	1.06
	250 (200)	0.85	1.23	1.17
DP12	50	1.20	1.72	1.76

[1] Relative concentration = concentration in drug product/ concentration in water

[2] Time zero is after an autoclave sterilization cycle

[3] NT = Not tested

[4] This drug was only tested at one time point, representing 24 months storage at 25ºC

[5] NMT 100 means the concentration of the target leachable in the drug product was less than the quantitation threshold of 100 ng/ml (ppb)

Conclusion:

Final design space established using QbD included:

- Aqueous drug product whose pH was 2-8 and had no polarity influencing agent
- Packaging component of same composition i.e. Polyolefin material
- Fill volume from 50-1000ml
- Product subjected to terminal sterilization and stored at room temperature for 24 months

It was found that any drug product which falls under this design space limits would considered to be compatible with packaging system and would be considered safe for human use.[41]

5.4 Case study IV: Presence of particulate matter in drug products

In parenteral formulations, presence of particulate matter or the extraneous substances that cannot be quantitated by chemical analysis are considered to be risky for patients. They may come from environment, equipment, raw materials, and ingredients of the formulation or particulate matters may also be formed in formulation as a result of interaction between drug product and packaging material. To prevent contamination from particulate matter, it is obligatory to have knowledge about drug product, raw materials and packaging material.

Presence of particulate matter in formulation may pose many serious problems for patients, if not detected earlier. Following consequences may arise if particulate matter is not handled/ monitored properly:

1) Large, hard, non-spherical particles can block blood flow which may result in emboli
2) Large, softer, spherical particles may collect accumulate in organs and causes damage to the tissues with the passage of time

Due to presence of particulate matter in formulation, various pharmaceutical industries had voluntarily recalled their products from US market.

Study 1: Dialysis solution is used in condition of acute and chronic renal failure. Particulate matter presence may after reacting with foreign particles cause local inflammation. On August 13, 2014, Baxter voluntarily recalled two lots (i.e. C940700 & C940841) of Dianeal low calcium Peritoneal Dialysis (PD) solution, due to the presence of PVC particulate matter, garment fiber and oxidized stainless steel.

Study 2: On January 27, 2012, Cephalon, Inc. had voluntarily recalled Treanda (Bendamustine HCl) injection 25 mg/ 8 ml, having lot no. TB30111. This injection is used for the treatment of Chronic Lymphocytic Leukemia (CLL). Batch was recalled due to presence of glass fragments in some vials of the same batch which may have caused emboli or tissue damage.

Study 3: On December 15, 2012, Hospira had voluntarily recalled three lots of Carboplatin injection due to presence of Carboplatin crystals in the vial. These crystals may block blood vessels and cause local infarction, vasculitis and thromboembolism.

Study 4: On January 20, 2015, Hospira had voluntarily recalled one lot (i.e. 44-002-JT) of Sodium Chloride injection0.9% (USP), 250ml due to the presence of human hair in the vial.

Study 5: On April 17, 2014, Hospira had voluntarily recalled seven lots (i.e. 29-614-DJ, 29-615-DJ, 29-616-DJ, 29-617-DJ, 29-628-DJ, 29-629-DJ & 29-630-DJ) of Propofol Injectable Emulsion due to presence of defects on vial neck and also due to metal particulates in the emulsion.

Source of particulates:

There are various sources for the origin of particulate matter and some of these are as follows:

1) Particulate matter may be present itself in the solution
2) May come from environment or equipment
3) May come from packaging material

Experts believe that increased use of protein therapeutic agents is also one of the reasons for development of particulates as a result of interaction between drug product and packaging material.

Remedial actions:

Several parenteral manufacturers have taken various steps to minimize the occurrence of particulate matter in dosage form which include optimization of QMS, starting from auditing of suppliers sample to final auditing of finished products for any contaminants.

There are several industries which are implementing risk management and QbD approach for reducing recalls. QbD approach is offering many advantages i.e. consistent and robust production of high quality products, thus reducing the chances of batch recalls.

Conclusion:

QbD approach adopted by glass manufacturers enables them to thoroughly understand the impact of process and material attributes on overall quality of the glass. By prior assessment of risk associated with the interaction between drug product and primary packaging material, all those variables which are going to influence the quality of glass manufactured and the finished product can be optimized. However, there are various challenges in adopting QbD approach. These include lack of understanding of QbD principles and its proper implementation in the industries. Time and cost are two factors that have hampered the implementation of QbD. Effective implementation of QbD in any process takes time and also incurred high cost.

So, it was concluded that with the proper utilization of QbD approach industry can avoid presence of particulate contaminants in drug products and further reduces the chances of batch recalls.[42,43,44,45]

5.5 Case study V: Regulatory submission

In 2005 USFDA introduced the CMC pilot program in Federal register as well as made it a part of pharmaceutical cGMP for the 21st century. The main motive behind the CMC pilot program was to demonstrate enhanced product and process understanding with the submission of CMC in NDA application and to gather feedback from various pharmaceutical industries to make any change or revision in FDA quality assessment guidelines. Enhanced process and product understanding promotes regulatory flexibility.

In this case study, "XYZ" pharmaceutical industry highlighted the changes or additions which an industry has to do in quality module of CTD dossier while submitting the QbD application for any product in this case product "A".

"XYZ" industry had submitted NDA application for product "A" to FDA under CMC pilot program. In response to it FDA had assigned a review team to review CMC section to give

any citation on it. Industry had several interactions with FDA and also with the agencies during Pre-Approval Inspection (PAI) and Pre-operational Visit (POV) at product manufacturing site and agency had given several suggestions and feedbacks to the company. This meeting had given company an idea regarding the content that should be included in the application during NDA review for facilitating the review process effectively. Topics which were discussed during interaction between FDA and "XYZ" industry are:

- Terminology used for describing QbD concept in the application
- Identification of CPPs and CQAs
- Quality Risk Management (QRM) approach utilized for identification of highly risky process parameters
- Development of design space with scale up changes
- Confirmation of design space at commercial scale
- Effect of equipment used and its design on design space and control strategy
- Regulatory strategies for managing changes (movement within design space)

While submitting the marketing authorization application of product "A" in counties other than US e.g. Europe, Canada, Japan, South Africa, Australia etc., industry had requested pre-submission meeting with concerned regulatory body e.g. it required meeting with EMEA PAT group for discussing its planned QbD approach for product "A". The interaction with FDA was found to be beneficial for industry and highlighted several points to be followed during submission and review process of product "A" for CMC pilot program following the QbD approach:

1) Comprehensive Quality Overall Summary (QOS): While reviewing NDA application, QOS was considered as the most important part of application. It served as roadmap for the review of dossiers effectively. It is the part of CTD format that provides summary of CMC aspects of an application. Information present in QOS should be concise and include information on the processes used for the identification of CQAs, CMAs and CPPs. It was also noticed that countries, other than USA, required traditional QOS rather than comprehensive QOS.
2) Pharmaceutical development report: QbD approach focused on enhanced process as well as product understanding. Pharmaceutical development report (3.2.P.2) section for drug

product and (3.2.S.2.6) section for drug substance demonstrated the enhanced understanding and enhanced reviewers confidence in applicant's manufacturing quality.

3) Raw material characterization: For process and product understanding complete information on characteristics of raw material used is important, which effects the manufacturing as well as overall quality of the drug products. Material testing is usually done to get good quality API, excipients and the test results should comply with the compendial test specifications. Control strategy should also be applied to excipients to ensure product performance.
4) Quality risk assessment: Quality risk assessment is the major part of product development by systematic approach. Risk assessment approach adopted by the sponsors for identifying and controlling risk should be clearly mentioned in the application. Terminology used for risk assessment should be properly defined in the application.
5) Scale-up process: During manufacturing process, design space suitable for commercial batches is also prepared to suit the product quality. Scale up strategy should also include all those factors which are going to vary while moving from pilot batch to commercial manufacturing. Proper strategy should be applied to control all the CQAs related to the drug substance and the drug product, to get quality product finally during commercialization. Parameters are also going to change with it, so, these parameters should be effectively controlled by adopting proper design space while producing batches in tons.

Conclusion:

For successful implementation of QbD, it is necessary to harmonize QbD concepts globally. Regular inspection by regulatory agencies, understanding of risk management concepts will further fastens the QbD utilization. Module 3 of dossier should include detailed information on product development with risk management approach, control strategy and design space used in the product manufacturing.[46]

Information related to QbD is submitted in the Module 3 of CTD in Pharmaceutical development section 3.2.P.2 (Table 5.5) as follows:[47]

Table 5.5: Module 3 containing QbD information[47,48]

CTD Section	Information
3.2.P.2	**Pharmaceutical development**
3.2.P.2.1	Components of drug product
3.2.P.2.1.1	Executive summary
3.2.P.2.1.2	Analysis of Reference Listed Drug (RLD)
3.2.P.2.1.3	Quality Target Product Profile
3.2.P.2.1.4	Critical Quality Attributes
3.2.P.2.1.5	Components of drug products
3.2.P.2.2	Drug product
3.2.P.2.2.1	Formulation development
3.2.P.2.2.2	Overages
3.2.P.2.2.3	Physicochemical and biological properties
3.2.P.2.2.4	Comparative testing between generic and RLD
3.2.P.2.3	Manufacturing process development
3.2.P.2.3.1	Description of manufacturing process
3.2.P.2.3.2	Development of critical unit operations
3.2.P.2.3.3	Comparison between manufacturing process used to produce registration stability batches and final commercial batches
3.2.P.2.4	Container closure system
3.2.P.2.5	Microbiological attributes
3.2.P.2.5.1	Container closure and packaging integrity
3.2.P.2.5.2	Antimicrobial effectiveness
3.2.P.2.5.3	Other microbiological attributes
3.2.P.2.6	Compatibility (with diluents or dosage devices)
3.2.P.2.7	Control strategy

3.2.P.2.7.1	Control strategy for drug product
3.2.P.2.7.2	Control strategy for raw material attributes
3.2.P.2.7.3	Control strategy for manufacturing process
3.2.P.2.7.4	Product lifecycle management and continual improvement

5.6 Case study VI: Implementation of QbD in present scenario

5.6.1 Percentage of ANDAs containing QbD element filed as per fiscal year

Pharmaceutical equivalence and the bioequivalence are the two parameters which are adopted to ensure the quality of generic products being filed for ANDA. FDA had given emphasis that this approach is used only for those formulations which are simple in design i.e. solutions and immediate release dosage forms, but for the complex delivery systems like transdermal delivery system, modified release dosage forms etc. such paradigm is utilized which ensures the quality of generic products**.** For this reason from January 2013 onwards, FDA had made it necessary to implement QbD while filing an ANDA. Percentage ANDAs containing QbD which are submitted in 2012 – 2013 are given in Table5.6.[12] In International Forum Process Analytical Chemistry (IFPAC) meeting (US), FDA CMC Reviewer Dr. Daniel Peng reported FDA's study regarding the generic industries who had started implementing QbD elements while filing ANDAs.[12,34]

Table 5.6: Percentage QbD implemented in ANDAs[12,34]

Month/ Year	**% ANDAs submitted with QbD adoption**
June 2012	24.6
July 2012	25.5
August 2012	53.3
October 2012	62.5
January 2013	82.9

5.6.2 Percentage of NDAs containing QbD element filed as per fiscal year

FDA had reported percentage increment in the filing of QbD from 2010 – 2011. Percentage increase in QbD implementation during NDA filing is given as per the different fiscal years in Table 5.7 and Figure 5.7.[35]

Table 5.7: Percentage QbD adoptions in NDAs (2010 – 2011)[35]

Time	NDA filed	NDA with QbD filed	Percentage
Oct. 2009	8	0	0
Nov. 2009	15	1	7
Dec. 2009	38	3	8
Jan. 2010	44	3	7
Feb. 2010	47	4	9
Mar. 2010	63	5	8
Apr. 2010	74	6	8
May 2010	84	6	7
June 2010	89	6	7
July 2010	99	8	8
Aug. 2010	103	8	8
Sept. 2010	111	9	8
Oct. 2010	5	0	0
Nov. 2010	16	1	6
Dec. 2010	31	3	10
Jan. 2011	41	4	10
Feb. 2011	50	4	8
Mar. 2011	60	5	8
Apr. 2011	71	5	7
May 2011	77	5	6
June 2011	86	5	6
July 2011	90	5	6

Time	NDA filed	NDA with QbD filed	Percentage
Aug. 2011	100	6	6
Sept. 2011	113	6	5

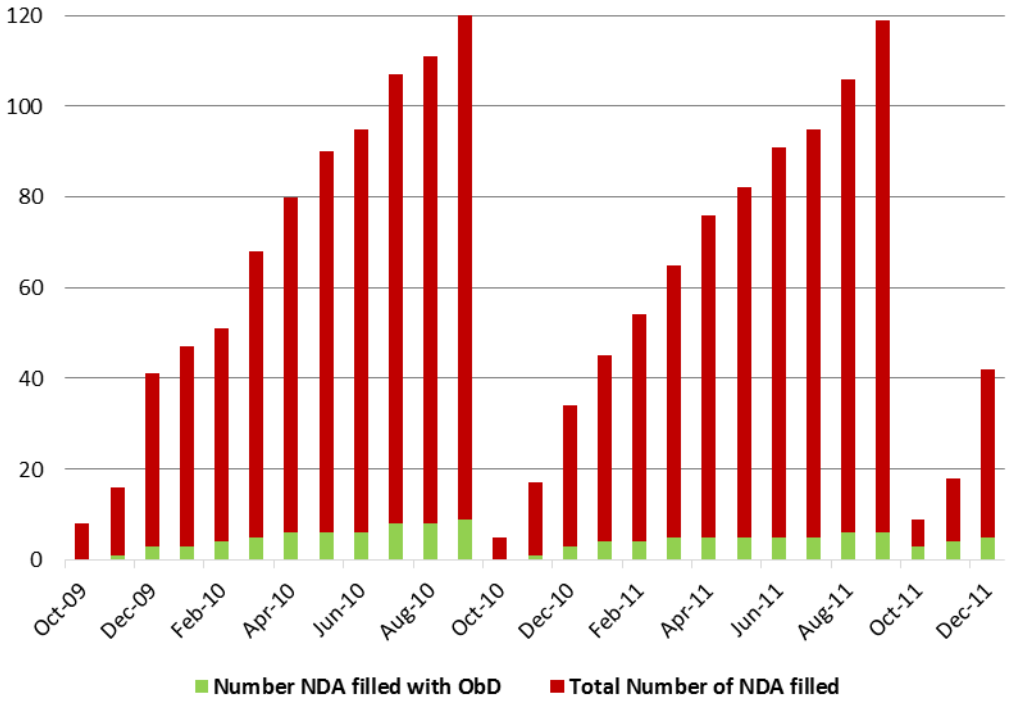

Figure 5.7: Percentage QbD adoption in NDAs (2010 – 2011)[35]

From 2013 onwards, FDA had made it compulsory to implement systematic approach while filing any NDA or ANDA application in CDER. Following data (Table 5.8) shows the NDA application filed between Jan 2014 – Jan 2015 which included QbD concept in their application for the manufacturing of drug substance or drug product.

Table 5.8: Drugs to which QbD approach is implemented (Jan 2014 - Jan 2015)[49]

S.No.	Drug	Applicant	NDA number	Formulation	Approval date
1	Farxiga	Bristol Meyers Squibb	202293	Tablet	Jan.8, 2014
2	Imbruvica	Pharmacyclics	205552	Capsule	Feb.12, 2014
3	Noxafil	Merck Sharp and Dohme Corp.	205596	Injection	Mar.13, 2014
4	Purixan	Nova Laboratories	205919	Oral suspensions	April 28, 2014
5	Zontivity	Merck Sharp and Dohme Corp.	204886	Tablet	May 8, 2014
6	Sivextro	Trius Therapeutics	205436	Injection	June 20, 2014
7	Olaparib	AstraZeneca Pharmaceuticals LP.	206162	Capsule	Dec.19, 2014
8	Zerbaxa	Cubist Pharmaceuticals	206829	Injection	Dec.19, 2014
9	Edoxaban Tosylate	Daiichi Sankyo	206316	Tablet	Jan. 8,2015

Conclusion:

FDA had made it compulsory to incorporate QbD approach while filing any dossier for authorization, as it provides higher level of assurance to product quality and increases efficiency of manufacturing process. It was observed that there was a subsequent increment (as shown in Figure 5.7) in QbD adoption, while filing NDA and ANDA during regulatory submission from year 2010 – 2013. QbD approach was also implemented in various formulations like in tablets, capsules, injections, suspensions etc by several pharmaceutical industries.

CHAPTER 6

SUMMARY AND CONCLUSION

CHAPTER 6

SUMMARY AND CONCLUSION

With the increase in market competition every pharmaceutical manufacturer aims to develop best quality product with or without minimum errors and defects. To achieve this objective QbD has been initiated and implemented. Better implementation of QbD in a process requires coordination and cooperation among production department and quality management department for thorough understanding of all the parameters related to it. ROW countries, i.e. semi regulated countries like India are lacking behind due to quality, safety and efficacy related issue of the drug products. For them this approach can work wonders by improving and assuring the quality of the products and can result in increased share value of ROW countries in the developed countries. From the year 2013 onward, US FDA has also made it mandatory to utilize QbD for pharmaceuticals in ANDA filing.

QbD is considered as a robust process, ensures quality and lowers the cost of production which is beneficial for both pharmaceutical industries as well as for the consumers. Researchers are taking initiatives to write the articles and journals on QbD for the benefit the fraternity of pharmaceutical industries as well as academics. Approximately 1785 publications had been published on QbD till April 2015. It is considered as a boon for generic manufacturers which can reduce time for scale up and facilitate regulatory approval. As per the survey study, it was observed that QbD enhances the process understanding (68.4%), increases product quality (66.7%) and reduces variation in products (57.9%). Almost 32% companies throughout the world are not implementing QbD. Reason cited for the same are:

- Lack of guidance from regulatory agencies (46.2%)
- Lack of understanding of its basic concepts (23.2%)

FDA remarked that during drug shortage workshop (Sept. 2011), it was observed that root cause for drug shortages were lack of process and product knowledge. As QbD enhances process and product understanding, we can overcome drug shortage in market by implementing this approach.

An increase of 8.4% in implementation of QbD has been observed from 2013 (43.7%) to 2014 (52.1%). By the end of 2020, QbD will help to increase the product yield from 70% to 90% with zero wastage.

CHAPTER 7

REFERENCES

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REFERENCES

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CHAPTER 8

PUBLICATION

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Review Article

QUALITY BY DESIGN (QBD) IN PHARMACEUTICAL INDUSTRY

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ABSTRACT

In 2004 US Food and Drug Administration (FDA), as part of the Process Analytical Technology Guidance, introduced the idea of Quality by Design (QbD). The core objective was to design quality into the process and product rather than try to check quality of the product at the end of production. It has been known since long time that "quality by testing" is a low-yield and costly strategy. ICH, in 2005, outlined the concept of design space in its Q8 guideline related to development of pharmaceuticals. Since that time, pharmaceutical companies, despite depending on innovation for their livelihood, have been adopting QbD for new drug applications (NDA) and as well as for Abbreviated New Drug applications (ANDA). In nutshell it has been observed that, now QbD is becoming mainstay of development of pharmaceutical products.

Key words: Quality, pharmaceuticals, FDA, ICH, industry

INTRODUCTION

QbD has its origins dating back to the 1950s when the initial ideas of the operating window (now called as "design space") in the Pharma and Biotech world were put forth (Box and Wilson 1951). Later in 1992, Juran popularized the term "Quality by Design" in his book. Some of the experts says that pharma and biotech are behind the times while others see that the 'glass is half-full' and that pharma and biotech can come up the learning curve much more quickly than other industries[1].

FDA's emphasis on QbD

In January 2011 FDA announced their new process validation guidance which leans heavily on the ICH documents, Q8, Q9 and Q10 stating, in the introduction that, "this guidance aligns process validation activities with a product lifecycle concept and with existing FDA guidance, including the FDA/International Conference on Harmonization (ICH) guidances for industry, *Q8 (R2) Pharmaceutical Development*, *Q9 Quality Risk Management*, and *Q10 Pharmaceutical Quality System*". Although this guidance does not repeat the concepts and principles explained earlier, FDA encourages the use of modern pharmaceutical development concepts, quality risk management, and quality systems at all stages of the manufacturing process lifecycle[2].

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In June 2011 FDA Center for Drug Evaluation and Research (CDER) updated its "Manual of Policy and Procedures" (MAPP 5016.1) to read regarding applying ICH Q8 (R2), Q9, and Q10 Principles to CMC Review[1,2].

The MAPP outlines and clarifies how the chemistry, manufacturing, and controls (CMC) reviewers in the Office of Pharmaceutical Science (OPS) should apply the recommendations in the ICH Q8 (R2), Q9, and Q10 guidance to industry. OPS CMC reviewers will consider ICH Q8 (R2), Q9, and Q10 recommendations when reviewing applications that may or may not include QbD approaches[3,4].

In 2012 FDA commented on the use of QbD in development of generic drugs.

"We encourage you to apply Quality by Design (QbD) principles to the pharmaceutical development of your future original ANDA product submissions, as of January 1, 2013. A risk-based, scientifically sound submission would be expected to include the following: Quality target product profile (QTPP), critical quality attributes (CQAs) of the drug product, product design and understanding including identification of critical attributes of excipients, drug substance(s), and/or container closure systems, process design and understanding including identification of critical process parameters and in-process material attributes control strategy and justification. Figure 1 portrays how FDA has implemented QbD in generic drugs[5-7].

Figure 1: Implementation of QbD by FDA

Resistance to QbD

Resistance to any new idea is a natural human reaction; resistance happens to all new ideas, not just QbD. In order to create and sustain use of QbD, it must be recognized that using QbD is a culture change and a well-planned initiative using a culture change strategies and models like that proposed by John Kotter (1996) must be utilized. Some critical building blocks include a strategy, a plan, QbD demonstration projects and periodic management review at several levels in the organization – strategic, managerial and operational[7,8].

Companies, large and small are adopting QbD and progress is being made. There continues to be conferences on the subject in the US, India and Europe. The subject is discussed frequently in the literature. ISPE (International Society for Pharmaceutical Engineering), among other organizations have developed best practices to guide its deployment. But there is much work to be done[8].

QbD provides a common language for outsourcing partnerships. One area that needs attention is outsourcing to CMOs (contract manufacturing organizations) which is on the increase. Some companies want to develop

partnerships to increase the effectiveness of CMO relationships. Partnerships are more easily praised than practiced and should be viewed as a something needs constant attention over its lifetime. Viewed as a continuing process requires a common language, common method of working together; both needed for the development of trust, an essential ingredient of a healthy partnership[9,10].

Figure 2: QbD is a continuing process.

QbD can also help create the approach and common language needed for developing the relationships required for successful outsourcing[4]. QbD is a disciplined and systematic approach for effectively creating and communicating the process understanding needed to develop, launch and operate compliant processes[6]. A holistic approach to QbD with a focus on how the needed process understanding is developed to enable effective process development, transfer, improvement and control. Improved communication and collaboration is developed as a natural by-product of using QbD. Quality by Design enables both sponsors and CMOs to increase competitiveness[6,7,9].

Technology transfer is also critical to successful Sponsor-CMO relationships. QbD can help here as well. The price paid by the Pharma Company to the CMO is a function of the risks involved including: technology transfer will be done rapidly and smoothly, manufacturing will be stable and capable. Risk is a function of process understanding - Ability to: predict process performance and move technical information between the parties. An effective strategy is to use QbD to build quality into critical processes thereby increasing process understanding and reducing risk. Some critical processes include: product and process design, technology transfer, manufacturing and process control and quality assurance and control[11,12].

QbD provides an in-built quality assurance for tech transfer, speedy process and reduced costs. Overall QbD is benefit at all level and for all level (figure 3). It also help in defining roles at all levels enhances communication and identifies the needed skills. Also included are structures for tech transfer at the tech transfer program level and individual tech transfer project level and the needed tech transfer management systems such as project selection and sequencing, management review, communication and recognition and reward, measurement system evaluation and the creation of the needed process understanding[13,14].

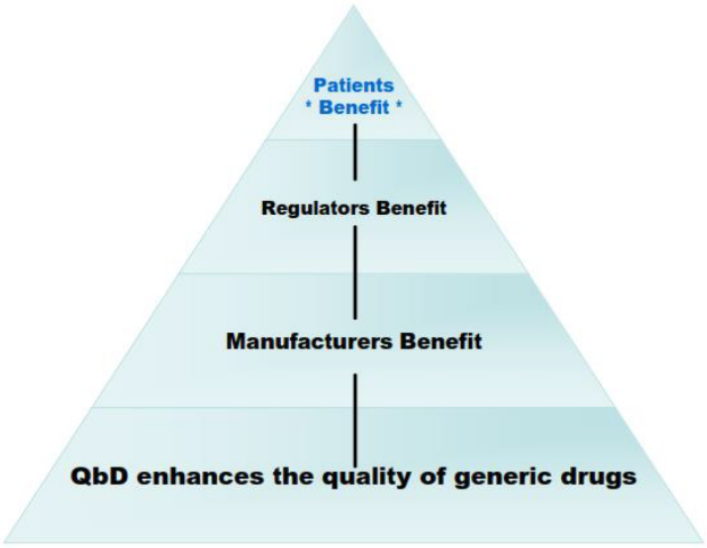

Figure 3: Benefits of implementing QbD

QbD: More than just a design

QbD must also be done effectively for the approach to deliver the promised benefits. An impression that one might get from reading the literature is that QbD is synomous with design of experiments (DOE). That all you need to do to implement QbD is to use DOE. Nothing could be further from the truth. DOE is an important tool of QbD but QbD has many more important building blocks such as process control, process robustness, failure modes assessment, etc.[4,6]

When developing models used to create the design space it is important to have a plan and strategy to guide the experimentation as summarized in Figure 4. This approach which was developed at DuPont in the 1960s and was used as an integral part of their QbD work speeding up the experimentation process, thereby increasing the probability the right data are collected at the right time[15].

Another important consideration is that the models used to develop the design space be confirmed before used to construct the design space (short-term validation). It is also critical that an ongoing process of model verification (long-term verification) be done as the manufacturing process operates. Such a process should be an integral part of the "Continued Process Verification" system that is an integral part of Stage 3 of the FDA's new process validation guidance.

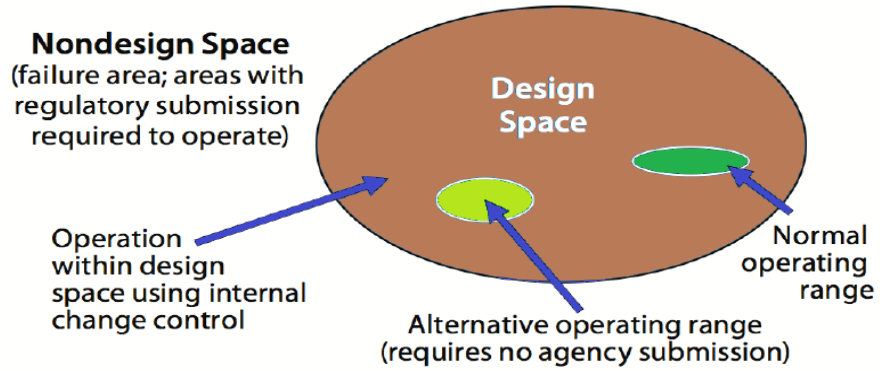

Figure 4: Positioning of design space and operating space.

Pharmaceutical equivalence and the bioequivalence are the two parameters which are adopted to ensure the quality of generic products being filed for ANDA. FDA had given emphasis that this approach is used only for those formulations which are simple in design i.e. solutions and immediate release dosage forms, but for the complex delivery systems like transdermal delivery system, modified release dosage forms such paradigm is utilized which ensure the quality of generic products[16-18].

At International Forum Process Analytical Chemistry (IFPAC) meeting, held in Baltimore (US), FDA CMC Reviewer/ QbD Liasion in the office of Generic Drugs, it was emphasized to implement QbD elements while filing ANDA for the pharmaceutical [1,2,5]. It was revealed that a steady increase in the inclusion of the elements of QbD in ANDA filling. Table 1 portrays the growing share of QbD element in ANDA filled.

Table 1: QbD in ANDA filings

Month/ Year	% ANDAs filled (with QbD element)
June 2012	24.6
July 2012	25.5
August 2012	53.3
October 2012	62.5
January 2013	82.9

CONCLUSION

Literature reports has shown that QbD is an effective method for developing new products and processes, enabling effective technology transfer, and the optimization and improvement of existing processes. QbD enables the development of process understanding that is fundamental to tech transfer, creation of design space and sustaining performance, process control and improvement systems and very important, the reduction of risk. QbD also provides a common language and methodology for working together - creating win-win partnerships

resulting in the promised regulatory flexibility, improved process performance and compliance and enhanced bottom-line results for all parties involved.

The implementation of QbD would also improve the quality of Chemistry, manufacturing, and controls information to be submitted in drug approvals. Above all it would surely enhance the assurance of quality in pharmaceuticals in the world market.

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