World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Published by Atom and Cell Publishers
Available online at: http://www.wjpsonline.org/
Review Article

A review on: Applications of pharmaceutical quality by design in product development

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Received: 26-10-2016 / Revised: 24-12-2016 / Accepted: 27-12-2016 / Published: 01-01-2017

ABSTRACT

Quality by Design (QbD) is the modern approach for quality of pharmaceuticals. QbD ensures the quality of Pharmaceuticals. In this review, the Quality by Design is described with the help of few applied examples. Important elements, benefits, opportunities and steps involved in Quality by Design for Pharmaceutical products are described in this review. ICH Guidelines are the foundation of Quality by Design. It is based on ICH Guidelines Q8 for pharmaceutical development, Q9 for the quality risk management, Q10 for pharmaceutical quality systems. QbD is applied in the pharmaceutical development and manufacturing of pharmaceuticals, analytical method development. The aim of the pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product. Quality cannot be tested into products but quality should be built in by design. It includes the Quality target product profile, critical quality attributes and key aspects of Quality by Design. It also gives comparison between product quality by end product testing and product quality by Quality by Design.

Keywords: Quality by Design (QbD), Elements of QbD, Process, Analytical Technology (PAT), Quality target product profile (QTPP), Design space, Risk assessment Methodology, Analytical Target Profile (ATP)

INTRODUCTION

The pharmaceutical Quality by Design (QbD) is a systematic approach for the development that begins with predefined objectives and it emphasizes on product and process for understanding and process control, based on sound science and quality risk management. Quality by Design (QbD) is emerging to enhance the assurance of safe, effective drug supply to the consumer, and also offers promise to significantly improve manufacturing quality performance. Even though the pharmaceutical industry has more focus on quality, it has failed to keep up with other industries in terms of manufacturing efficiency and productivity.

Before implementation of QbD in the pharmaceutical industry the practice was to carry out off- Off-line analysis for in-process testing as per the product specific need and product specifications were considered as the primary means of control. This was resulted in unpredictable scale up issues. Also the cost of revalidation and supplementary approvals was used to be more. But now due to implementation of QbD the scenario is changing. The Pharmaceutical industry has now started using systematic approach to development that begins with predefined objectives and emphasizes on products and process understanding for process control. This new approach is illustrated in fig. 1. [1,2, i]

Design: Design Refers to a plan or convention for construction of an object or a system and its aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver to the intended performance of the product. Traditionally, the relationship between product attributes to product quality has not been well understood, and thus for the regulatory agencies has ensured quality via tight specifications based on observed properties of exhibit or clinical trial batches and constraining sponsors which use a fixed manufacturing process. Pharmaceutical quality always refers to product free of contamination and it's reproducibly delivers the therapeutic benefit promised in the label to the consumer. Hence quality by design relates to product performance of pharmaceutical quality as a product that is free of contamination and

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reproducibly it deliver the therapeutic benefit promised in the label to the consumer [2-6]

Pharmaceutical Quality by Design: Quality by Design (QbD) it is a systematic approach to pharmaceutical development that begins with predefined objectives which emphasizes product and process understanding and process control, it will based on sound science and quality risk mitigation assessment. It means designing and developing formulations and manufacturing processes for ensure a predefined quality. Thus, QbD requires an understanding how formulation and process variables influence product quality. As per ICH Q8 defines quality as the suitability, of either a drug substance or drug product for its intended use. Pharmaceutical QbD is a systematic, scientific, risk based, holistic and approach to pharmaceutical development that begins with predefined objectives and emphases product and processes understanding and process control. It means designing and developing formulations as well as manufacturing processes to ensure predefined product quality objectives. A Knowledge management and quality risk management this are two of the primary enablers of QbD. They are instrumental in achieving product realization, establishing and maintaining a state of control, and lastly facilitating continual improvement. QbD tools are shown in table 1. These tools are described in ICH quality guidelines Q8, Q9 and Q10. Quality risk management is one of the tools that provide proactive approach to identifying, scientifically evaluating, and controlling potential risks to quality. It also facilitates continual improvement in that product and process performance throughout the product life cycle. A Knowledge management it is a systematic approach to acquire, analyze, store, and disseminate all the information related to products, processes, and its components. This will also emphasize on a transparency of information from development to commercial and vice versa. [3,iii]

Table-1: QbD: Regulatory tools [2, 7,8]

Date	Guideline reference	Scope
Aug 2009	ICH Q8	Pharmaceutical development
Nov 2005	ICH Q9	Quality risk management
Jun 2008	ICH Q10	Pharmaceutical quality system
Jan 2011	FDA	Process validation. General principal and practices
Dec 2011	ICH Q8/Q9/Q10	Guide for implementation
March 2012	EMA/CHMP/QWP/811210	Real time release testing
March 2012	EMA/CHMP/QWP/CVMP/70287 (draft)	Process validation
May 2012	ICH Q11	Development and manufacture of Drug substance

Comparison between traditional and QbD approach: The distinction between current approach and QbD approach is given in table 2. Pharmaceutical development, manufacturing process control and control strategy can be systemically defined and achieved with the use of QbD approach. This is further illustrated in the figure 2. By using QbD it can be ensured that the final product will always meet the predefined specifications avoiding the risk of rejection of batch due to noncompliance.[9,i] Whereas in Quality by end product testing approach, as shown in figure 3, there are more chances of batch failure and if the end product testing gives noncompliance the batch needs to be rejected resulting in serious consequences.

Table:2 Traditional approach & Enhanced QbD approach [i]

Aspects	Current	QbD
Pharmaceutical Development	Empirical, Random, Focus on optimization	Systematic, Multivariate experiments, Focus on control strategy and robustness
Manufacturing Process	Fixed	Adjustable within design space, managed by company's quality systems
Process Control	Some in-process testing	PAT utilized, Process operations tracked and trended
Product Specification	Primary means of quality control, based on batch data	Part of the overall quality control strategy, based on desired product performance
Control Strategy	By testing and inspection	Risk-based control strategy , real-time release possible

ELEMENTS OF QBD

In This section it describes the various elements in detail and provides examples of the elements for the controlled release (CR) products. An example of this would be drug substance particle size distribution (PSD) or bulk density that may affect the flow of a granulation and therefore the manufacturability of the drug product. Similarly, the dissolution from a controlled release dosage form it is dependent on the particle size of the polymer and its hardness of tablet. In this example, PSD and hardness can be designated as CQA's. [10,11] They can also commonly referred to as critical material attributes (CMA). Figure 3 provides a pictorial representation of the typical elements of QbD. This section describes the various elements in detail and provides examples of the elements for controlled release (CR) products. [12]

QbD development process include: [i]

- Description of a quality target product profile that describes the use, safety and efficacy of the product. It defines a target product quality profile that will be used by formulators and also process engineers as a quantitative surrogate for aspects of clinical safety and efficacy during the product development.
- Gathering of all relevant prior knowledge about the drug substance, potential excipients possibility of drug excipient interactions and process operations into a knowledge space. Risk assessment may be used to prioritize knowledge gaps for further investigation
- Designing a formulation and identification of the critical material (quality) attributes for the final product that must be controlled to meet the target product quality profile.
- Identification of the critical process parameters and input (raw) material attributes that must be controlled to achieve the final product of the desired quality. Using risk assessment it prioritizes process parameters and material attributes for experimental verification.
- Combining prior knowledge with experiments to establish a design space or other representation of process understanding.
- Establishing a control strategy for the entire process that may include input material controls, process controls and monitors, design spaces around individual or multiple unit operations, or final product tests. The control strategy should be encompassing expected changes in scale and can be guided by a risk assessment.

Design of experiments (DOE),risk assessment ,and process analytical technology (PAT) they are the tool that may be used in QbD process where appropriate. They are not check-box requirements.[i]

QUALITY TARGET PRODUCT PROFILE (QTPP): QTPP is a prospective summary of the quality characteristics of a drug product that is to be ideally achieved to ensure further desired quality, taking into account safety and efficacy of the drug product [1-2].More recently an expanded use of the TPP in this development planning, clinical and commercial decision making, regulatory agency interactions, and risk management has started to evolve. The TPP can be play major central role in the entire drug discovery and development process such as:[9,10]

1. For Effective optimization of a drug candidate
2. To Take Decision-making within an organization
3. To Design of clinical research strategies, and
4. To Constructive communication with regulatory authorities.
5. The TPQP guides formulation scientists to establish formulation strategies and it will keep the formulation effort to be focused and efficient. For example,(Table 3) a typical QTPP of an immediate release for solid oral dosage form would include: Tablet Characteristics and Identity Assay and Uniformity Purity/Impurity Stability, and Dissolution.

Table 3: Example of QTPP for a Typical Oral Controlled Release [12, 15-17]

Summary Quality Target Product Profile And identification of critical Quality Attributes For a typical oral controlled release Product		
Quality attributes	Target	Criticality
Dosage Form	Dosage form could be matrix tablet, maximum weight XX mg	
Potency	Dosage form label claim	
Dosing	One tablet per dose, once daily	
Pharmacokinetices	For example, controlled release over a period of 12 or 24 hr	Related to dissolution
Apperance	Dosage form description	Critical
Idendity	Positive for drug name	Critical
Assay	95.0-105.0%	Critical
Impurities	List specified impurities with appropriate limit; unspecified impurities with limit; total impurities with limit	Critical
Water	Current limit (eg., NMT 1.0%)	Critical/Not critical depending on API sensitivity to moisture
Content uniformity	Meets USP/EP/other pharmacopoeia	critical
Hardness	NLT X SCU (preferred for film coating) for a tablet	For example, can be, critical if related to dissolution
Friability	Current limit (eg., NMT 1.0%)	
Dissloution	Conforms to USP (eg., use a 5 point profile or NLT 10% in 0.1 N HCl for enteric coated tablets)	Typically critical
Microbiology	If testing required, meets harmonized ICH criteria	Critical only if drug product supports microbial growth

Design of Experiment: Design of experiments (DOE) is a systematic method to determine the relationship between factors affecting a process and the output of that process. In other words, it is used to find cause-and-effect relationships. This information is needed to manage process inputs in order to optimize the output. An understanding of DOE first requires knowledge of some statistical tools and experimentation concepts. Although a DOE can be analyzed in many software programs, it is important for practitioners to understand basic DOE concepts for proper application.[vii] For example parameters that affect the coating process are given in Figure-5. [14] Critical parameters are considered as independent variables in DOE.

DESIGN SPACE

ICH Q8 (R2) defines Design space as, the multidimensional combination and interaction of input variables (e.g. material attributes) and process parameters that have been demonstrated for provide assurance of quality. It will Working within the Design space is not be considered as a change, Movement out of the Design space it is considered to be a change and would normally initiate a regulatory post-approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval. Thus Design space is potentially scale and equipment-dependent, the Design space determined at the laboratory scale may not be relevant to the process at the commercial scale. Therefore, In Design-

space verification at the commercial scale becomes essential unless it is demonstrated that the Design space is scale-independent. [8,iii] For the development and refinement of the Design Space it begins at product conceptualization and continues to evolve throughout the lifecycle of the product. At the time of filing a submission, the Design Space can be considered to be a snap-shot in the time of representative of the current process knowledge. It continues to evolve as additional knowledge and information is generated during the commercialization of the product, which may lead to post-approval changes. Movement out of the Design Space is considered to be a change and would be normally initiate the regulatory post approval change process.[9,10]

A design space would be constructed for a single unit operation and multiple unit operations, or for the entire process. For the Submission of a design space to FDA is a pathway for obtaining the ability to operate within that Design space without further regulatory approval.[15]

Ex: Manufacturing changes within the approved design space without further regulatory and its review.

- Reduction for post-approval submissions.
- Better innovation due to the ability to improve processes without resubmission to the FDA when remaining in the Design Space.
- It more efficient technology transfers to manufacturing.
- Greater regulator for confidence of robust products.
- It gives Risk-based approach and identification.
- Innovative process for validation approaches.
- Less intense for regulatory oversight and less post-approval submissions.
- For the consumer, it gives greater drug consistency.
- It gives more drug availability and less recall.
- It Improved yields, lower cost, less investigations, reduced testing, etc.
- It takes Time to market reductions: from 12 to 6 years realized by amongst others.
- First time right: lean assets management.
- It is Continuous improvement over the total product life cycle (i.e. controlled, patient guided variability).
- Absence of the design freeze (no variation issues).
- It takes less validation burden.
- Real time controls (less batch controls).
- Realistic risk perceptions.[i]

A Design space is an only way to represent the process which understanding that has been established. The benefits of having a Design space are clear; there is one challenge to the effective use of a Design space is the cost of establishing it.[13]

Manufacturing changes within the approved design space It contributes substantially to realize the better, cheaper and safer mandate. [19,iii]

RISK ASSESSMENT METHODOLOGY FOR QBD : A systematic process for the assessment and control, communication and review of risks for the quality of the drug (medicinal) product across the product lifecycle which is called as quality risk management methodology. Risk assessment is a helpful science-based method, which used in the quality risk management that will help in

Identifying the material attributes and its process parameters that potentially have an effect on

Product CQAs. Risk assessment it based on typically performed in the pharmaceutical development process and it repeated as more information becomes available and greater knowledge is obtained. In QbD, the team of the scientist utilizes in the risk assessment tools in the R&D lifecycle.

Decision taken based on this technique generally impact on quality and its costs attributes to a

Much greater extent than which decisions made during process development and later in the product lifecycle. Risk assessment tools can be used to identify and level parameters (e.g., for process, equipment, input materials) with its potential to have an impact on product quality, based on their prior knowledge and primary experimental data. Once the parameters are identified, they can be further studied (e.g., through a combination of design of experiments, Mathematical models, or studies that lead to mechanistic understanding) for the achieve a higher Level of process its understanding. The pharmaceutical industry and its regulators can evaluate and manage the risks by using well-known risk management tools and internal procedures such As,

- Basic risk management facilitation methods (flowcharts, check sheets etc.);
- Failure Mode Effects Analysis (FMEA)[9]

The Design of Extended Release (ER) Coated Beads is illustrated in figure 6. It possess an inert core loaded with drug substance. These beads are further coated with a rate controlling polymer for obtaining the desired release profile. The ER beads, and IR granules and extra granular excipients were compressed into scored tablets. Multi-particulate ER portion performance depends on the choice of excipients such as the coating polymer, plasticizer

and anti-tacking agent. Initial selection of the polyvinyl acetate (PVAc) as the coating polymer, TEC as the plasticizer, and talc as the anti-tacking agent in the formulation was based on process requirements, a literature survey and previous experience. In the initial risk assessment of the ER polymer coating formulation variables which are shown inTable no:4 .ER excipient type, level and material attributes were evaluated in order to identify formulation variables with its high risk. Justification for the risk ranking is presented in all the formulation variables identified as the high risk was further studied to reduce the level of risk to an acceptable level.[19]

Table 4: Initial risk assessment of the ER polymer coating formulation variables

	ER Polymer Coating Formulation Variables						
ER coated beads CQAs	**Theoretical polymer coating level**	**Polymer aging**	**Polymer lot-to-lot variability**	**Additional pore former level**	**Plasticizer level**	**Anti-tacking agent level**	**Viscosity of coating dispersion**
Drug release	High	High	Medium	High	High	Medium	Medium
Drug release – alcohol induced dose dumping	High	High	Medium	High	High	Low	Medium

CONTROL STRATEGY

A planned set of controls, derived from current product and process for the understanding that ensures process performance and also product quality. The controls include parameters and its attributes related to the drug substance and drug-product materials and components, facility and equipment operating conditions, in-process controls, finished-product specifications, and this associated methods and frequency of monitoring and control.

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

There are Control Strategies which establishes the necessary controls - based on patient requirements – and it will be applied throughout the whole product lifecycle from product and process design through to final product, including the API and Drug Product manufacture, packaging and distribution. [9]

Product Lifecycle Management: Process performance can also be monitored to ensure that it is working as the anticipated for deliver product quality attributes as per predicted by the design space. This monitoring could include trend analysis of the manufacturing process as additional experience is gained during routine [13]

ATP (ANALYTICAL TARGET PROFILE)

ATP is identification which includes the selection of method requirements such as target analytes (product and impurities), analytical technique category, and product specifications. In that initial risk assessment would be performed for anticipation of the method requirements and analytical criticalities. General ATP for analytical procedures is as follows:

(a)target analytes selection (API and impurities)
(b)technique selection (HPLC, GC, HPTLC, Ion Chromatography, chiral HPLC, etc.)
(c)method requirements selection (assay or impurity profile or residual solvents).

This can be illustrated with the hel of example of a model synthetic route with ATP impurities. This synthetic route has been considered for analytical method development by HPLC/UPLC, HPTLC, or GC techniques with AQbD implementation. This synthetic route has eight steps from the starting material. Additional new raw materials are added at stages 4 and 6. Byproducts are forming at stages 5 and 7. Stage 4 product is a degradation of final drug substance. Stage 6 is a carryover to final Design Space. [vi]

Bhat et. al. [22] have reported the application of QbD for analytical method development. They described the development of a comprehensive science and risk based HPLC method and subsequent validation for the analysis of zidovudine active pharmaceutical ingredient (API). An efficient experimental design based on systematic scouting of all three key components of the RP-HPLC method (column, pH and mobile phase) is presented. They used the four step approach wherin first step goals of HPLC method development have to be clearly defined, in second step experimental design was used to assist with obtaining in-depth method understanding and performing optimization. In third step the experimental results were evaluated to select the final method conditions. Finally in fourth step the robustness and ruggedness was established.

QbD activities within FDA

Following activities are guiding the overall implementation of QbD:

In FDA's Office of the New Drug Quality Assessment (ONDQA), in new risk-based pharmaceutical quality assessment system (PQAS) was established based on the application of product and process understanding.[7, 11]

- Implementation for a pilot program to allow manufacturers in the pharmaceutical industry to submit information for a new drug application it demonstrating use of QbD principles, product knowledge, and process understanding. In 2006, Merck & Co.'s Januvia became the first product approved based upon their application.
- Implementation its Question-based Review (QbR) Process has occurred in CDER's Office of Generic Drugs.
- CDER's Office of Compliance has played an active role in complementing the QbD initiative by optimizing pre-approval of inspectional processes to evaluate commercial process feasibility and determining for if state of process control is maintained throughout the lifecycle, it will in accord with the ICH Q10 lifecycle Quality System.
- For Implementation of QbD for a Biologic License Application (BLA) is progressing.[i,7]

While QbD will provide better design for predictions, there is also a strong recognition for industrial scale-up and its commercial manufacturing experience will provides new and very important knowledge about the process and the raw materials which used therein. FDA is aware from the knowledge is not static and builds throughout the manufacturing lifecycle. FDA's release of the Process Validation as per guidance in January 2011 notes the need for companies to continue for the benefiting from knowledge gained, and it continually improve throughout the process lifecycle by making of adaptations to assure root causes of the manufacturing problems are quickly corrected With This vigilant and nimble approach is explained by FDA to be essential for best protect the consumer (patient). [11,i]

INTERNATIONAL CONFERENCE ON HARMONIZATION. (ICH)

Technical Requirements for Registration of Pharmaceuticals for Human Use. (ICH) [23]

- Pharmaceutical Development Q8 (R2)
- Quality Risk Management Q9
- Pharmaceutical Quality System Q10

The difference between QbD for the NDA and ANDA products it will most apparent at the first step of the process. For an NDA, the target product profile it comes under development while for the ANDA product and target product profile is well established by the labeling and clinical studies conducted for the support the approval of the reference product. [5,i,iii-v]

Advantages of Quality by Design

Benefits for Industry:

- It is important for Better understanding of the process.
- It gives less batch failure.
- It is more efficient and effective control of change.
- Return on investment / cost savings.
- **Additional opportunities:**
    - QbD approach it will enhance to pharmaceutical development provides opportunities for more flexible regulatory approaches. [1, 14, 23-24]

CONCLUSION

The Quality by design (QbD) is a best approach to encourage and support quality and to increase the further thinking about the best ways. While QbD is most effective when it is employed at a product/process design level, it should also be accomplished in the manufacturing and quality assurance environments. Modern quality system would be critical to support QbD and continuous improvement of pharmaceutical products over their lifecycle. Quality by design is an essential part of the modern reliable concept and is an innovative approach towards the pharmaceutical quality. Application of QbD principles facilitate development of quality products and their assessment throughout their lifecycle, and ultimately, result in greater patient benefit.

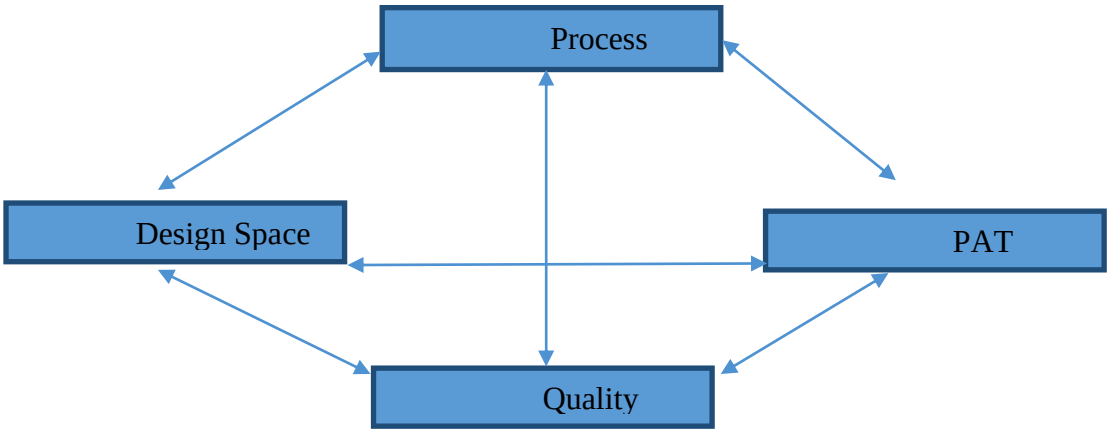

Figure 1: Process control [i]

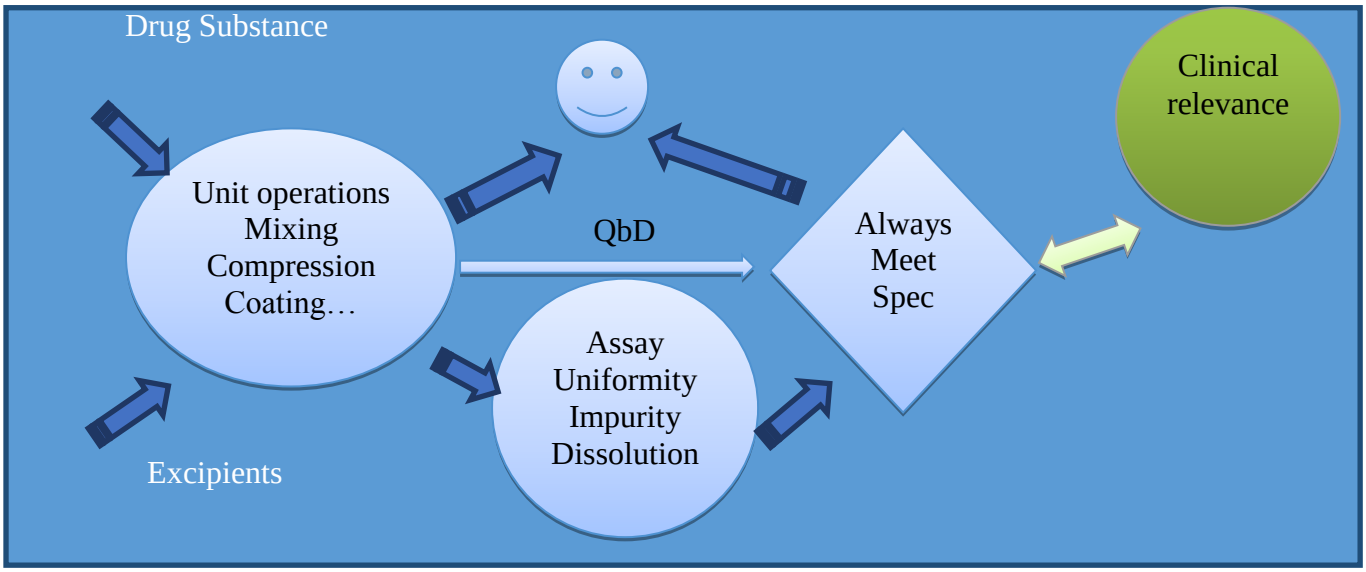

Figure 2: Quality by Design [i]

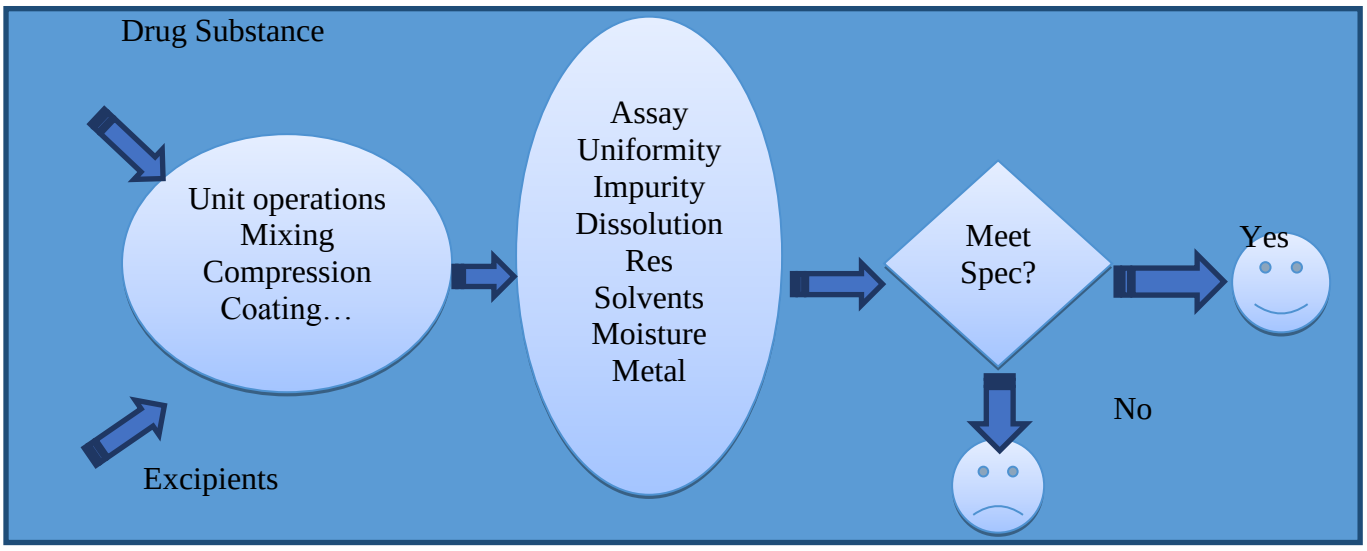

Figure 3: Quality by End Product Testing [i]

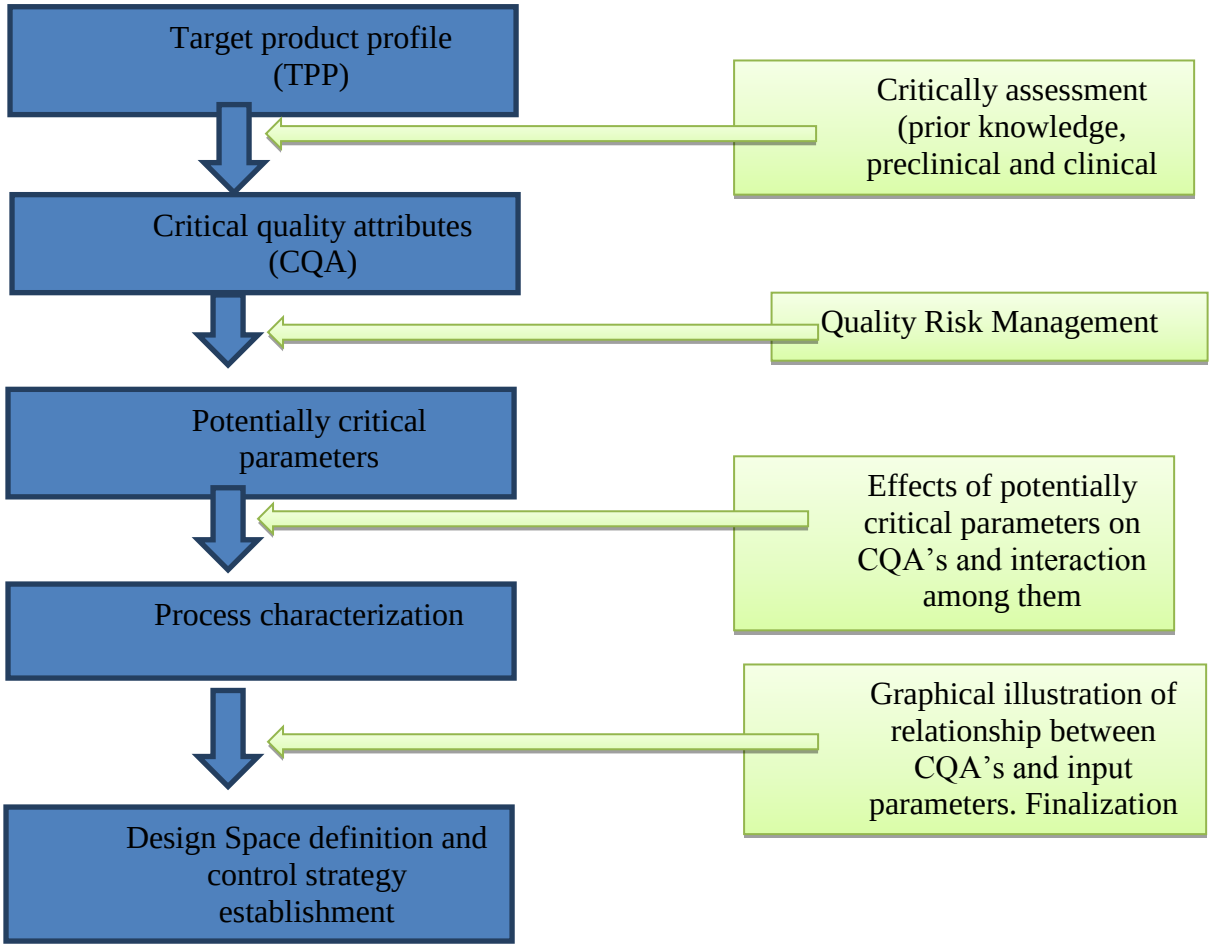

Figure 4: Flow chart for Product Quality by design. [3, 13, 14]

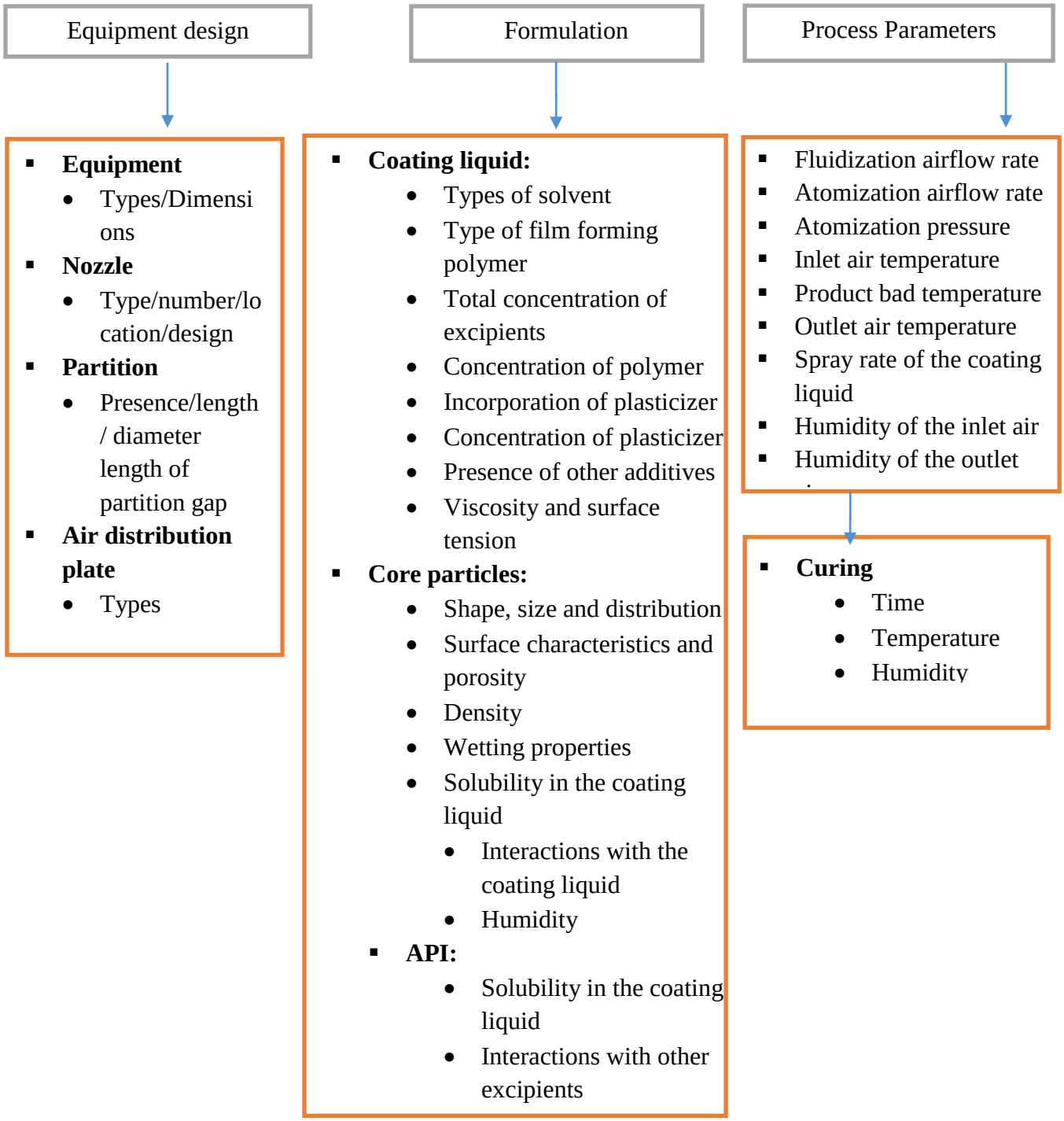

Figure 5: Parameters of the coating process [1,14]

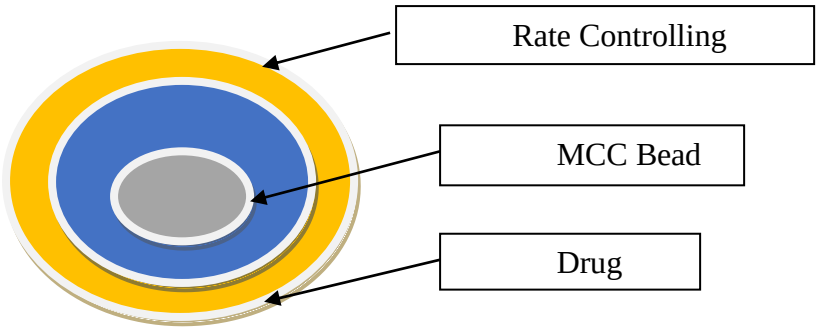

Figure 6: Structural representation of ER beads

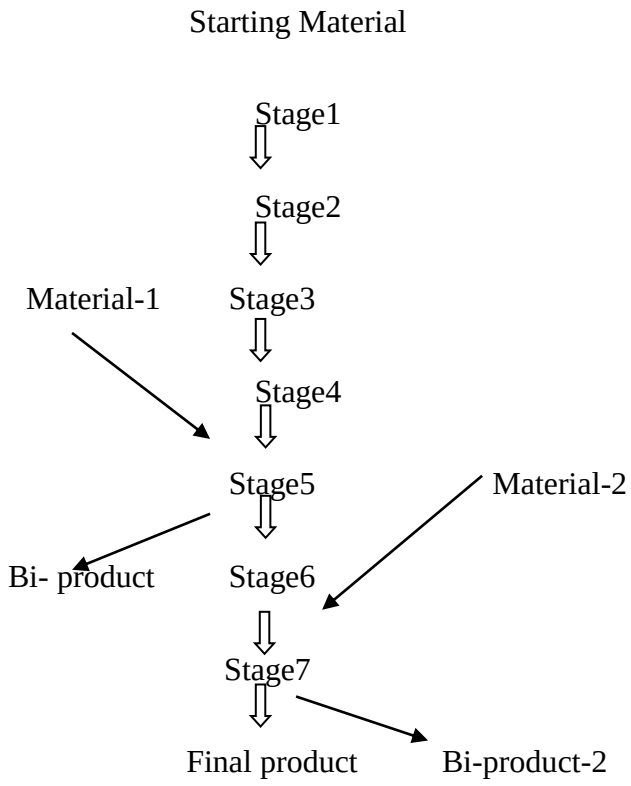

Figure 7 :Analytical QbD(AQBD) relation with Synthetic Development[vi]

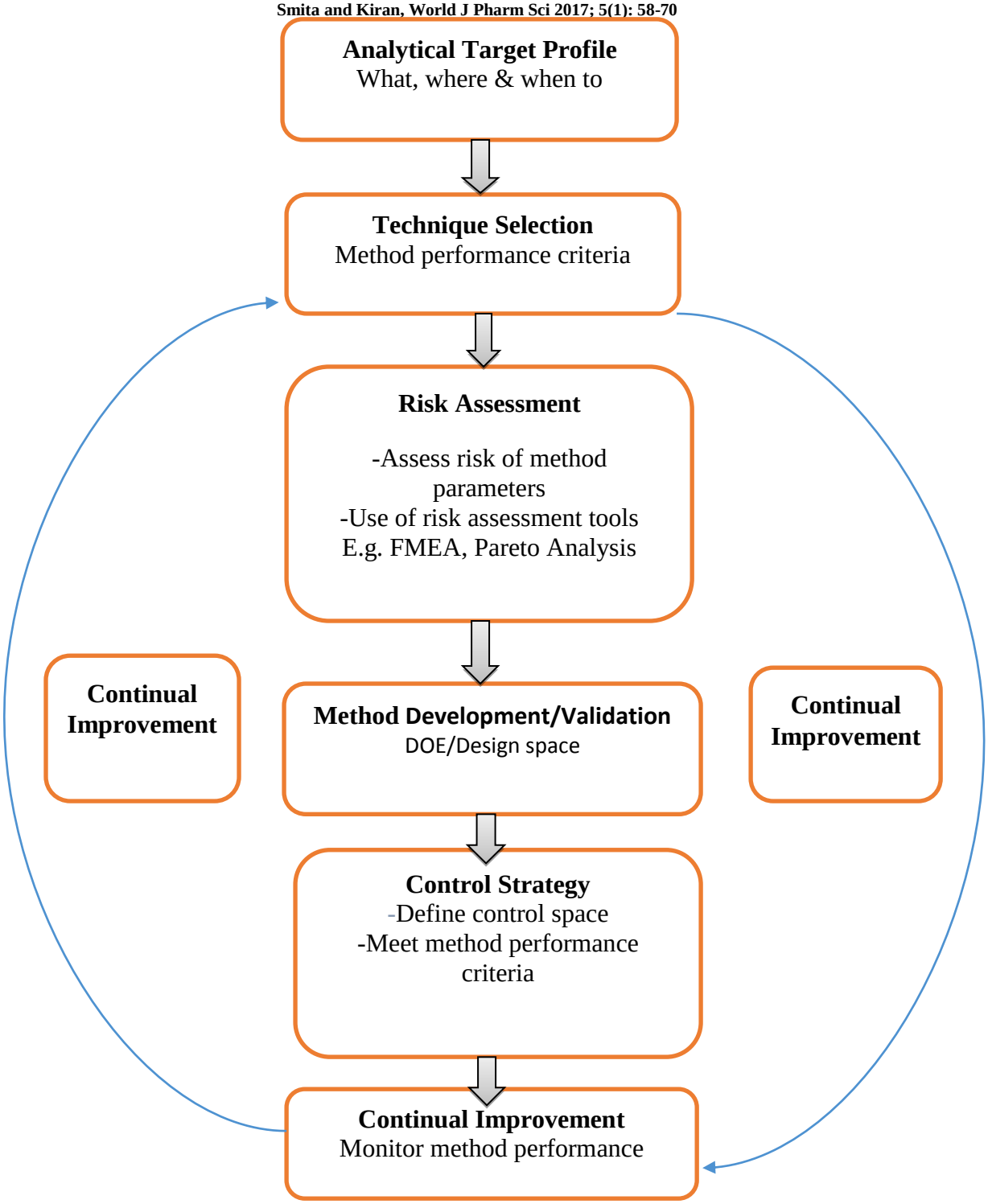

Figure 8: Analytical method development in QbD [11,13,20]

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