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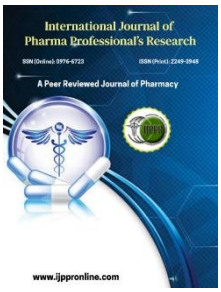

Quality By Design: Concept and Applications

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ABSTRACT:

Quality by design it is an approach in order to achieve quality of product in terms of customer satisfaction for pharmaceuticals. By this review we just summarised concept of quality, which is basically concerned with reliability, timely performance and economic of product. According to Sir Joseph Moses Juran "Quality could be planned and most quality associated problems have their origin in the way in which quality was planned in first place. It is based on ICH guidelines Q8 for pharmaceutical development, Q9 for quality risk management,Q10 for pharmaceutical quality system. It also compares between product quality by end product testing and by quality design. USFDA has consistently working on this matter in order to implement them on pharmaceutical industry. QbD advantages involves robustness of process, successful completion, scope for invention, enhanced understanding of method besides advantages, several disadvantages associated are internal unwillingness of industries, lack of belief in business core more time to file for generic products lack of technology to implemen

Introduction:

The basic concept of QbD is "The Quality cannot be tested into the product, but it should be built into it." The design space is defined as a manufacturing area of the product including Equipment, Material, and Operators and Manufacturing Conditions. The design space should be well defined prior to regulatory approval. Working with design space is not considered as a change, but working out of design space is considered as a change.[2]

Definition [FDA PAT Guidelines, Sept. 2004]

A system for designing, analyzing and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes of new and in-process materials and processes, with the goal of ensuring final product safety.[2]

The concept of "Quality by Design" (QbD) was defined as an approach which covers a better scientific understanding of critical process and product qualities, designing controls and tests based on the scientific limits of understanding during the development phase and using the knowledge obtained during the life-cycle of the product to work on a constant improvement environment.

Quality- by-design (QbD) is a concept introduced by the International Conference on Harmonization (ICH) Q8 guideline, as a systematic approach to development, which begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. Predefined objectives make up the quality target product profile (QTPP), that is, the summary of the drug product quality characteristics that ideally should be achieved.[3]

Pharmaceutical quality by design: Pharmaceutical QbD is a systematic, scientific, risk-based, holistic and proactive approach to pharmaceutical development that begins with predefined objectives and emphases product and processes understanding and process control. It means designing and developing formulations and manufacturing processes to ensure predefined product quality objectives (9). QbD identifies characteristics that are critical to quality from the perspective of patients, translates them into the attributes that the drug product should possess, and establishes how the critical process parameters can be varied to consistently produce a drug product with the desired characteristics. In order to do this the relationships between formulation and manufacturing process variables (including drug substance and excipient attributes and process parameters) and product characteristics are established and sources of variability identified. This knowledge is then used to implement a flexible and robust manufacturing process that can adapt and produce a consistent product over time. Thus, some of the QbD elements may include:

– Define target product quality profile

– Design and develop product and manufacturing processes

– Identify critical quality attributes, process parameters, and sources of variability

– Control manufacturing processes to produce consistent quality over time

Under the QbD paradigm, pharmaceutical quality for generic drugs is assured by understanding and controlling formulation and manufacturing variables. End product testing confirms the quality of the product and is not part of the manufacturing consistency or process control. Under QbT a product specification is often set by observing data from a small number of batches believed to be acceptable and then setting acceptance criteria that required future batches to be the same. Under QbD consistency comes from the design and control of the manufacturing process and the specification of drug product under QbD should be clinically relevant and generally determined by product performance.

The specifications for assay and dissolution often evaluate the most important characteristics drug products must have to ensure their effectiveness. It is interesting to note that the assay limit is currently determined in a manner that is closer to the QbD approach than to the QbT approach. The assay limit is normally set to be 90–110% with the exception a few selected drugs where there are clinical reasons for narrower acceptance limits, for example, 95–105%. Assay limits are not routinely set by using batch data. A sponsor that routinely produced drug product with an assay of 98–100% would still expect an assay limit of 90–110%.

However current dissolution acceptance limits are selected based on data from a small number of batches in the context of
their ability to distinguish batches with limited regard to clinical relevance. Under the QbD, the dissolution tests should be
developed to reflect in vivo performance as much as possible. For example, the acceptance criteria for BCS Class I and III
IR tablets may be much wider than that from batch data because, for these BCS classes, dissolution is highly unlikely to
be the rate limiting step in vivo (5). Similarly, dissolution tests for BCS Class II and IV drugs may need to be carefully
examined to better reflect in vivo dissolution (6).

The specification for impurities assesses another important characteristic a drug product must have to ensure its
safety. Under the QbD, the acceptance criterion of an impurity should be set based on its qualification/biological safety
level instead of the actual batch data. The biological safety level is generally determined by safety and/or clinical studies
although it may be also determined by toxicity studies (7).Therefore, the acceptance criteria for impurities are usually
those found in clinical study materials or reference listed drugs for generic drugs (7,8).

Define Target Product Quality Profile

The target product profile (TPP) is generally accepted as a tool for setting the strategic foundation for drug
development—"planning with the end in mind." More recently an expanded use of the TPP in development planning,
clinical and commercial decision making, regulatory agency interactions, and risk management has started to evolve. The
target profile is a summary of the drug development program described in the context of prescribing information goals. The TPP can play a central role in the entire drug discovery and development process such as: (1) effective
optimization of a drug candidate, (2) decision-making within an organization, (3) design of clinical research strategies, and
(4) Constructive communication with regulatory authorities. TPP is currently primarily expressed in clinical terms such as
Clinical pharmacology, indications and usage, contraindications, warnings, precautions, adverse reactions, drug abuse and dependence, over dosage, etc. Thus, it is organized according to key sections in the product's label. TPP therefore
links drug development activities to specific statements intended for inclusion in the drug's label.

Target Product Quality Profile (TPQP) is a term that is a natural extension of TPP for product quality. It is the quality
characteristics that the drug product should possess in order to reproducibly deliver the therapeutic benefit promised in the
label. The TPQP guides formulation scientists to establish formulation strategies and keep the formulation effort focused
and efficient. TPQP is related to identity, assay, dosage form, purity, stability in the label. For example, a typical TPQP of an
immediate release solid oral dosage form would include ():
– Tablet Characteristics
– Identity
– Assay and Uniformity
– Purity/Impurity
– Stability, and
– Dissolution

The TPQP of a generic drug can be readily determined from the reference listed drugs (RLD). Along with other available
information from the scientific literature and possibly the pharmacopeia, the TPQP can be used to define product specifications
to some extent even before the product is developed. Predefined, high quality product specifications make the product
and process design and developmentmore objective and efficient.

Design Product and Manufacturing Processes

Product Design and Development

In order to design and develop a robust generic product that has the desirable TPQP, a product development scientist must give serious consideration to the biopharmaceutical properties of the drug substance. These biopharmaceutical properties include physical, chemical, and biological proper-ties. Physical properties include physical description (particle size, shape, and distribution), polymorphism, aque-ous solubility as function of pH, hygroscopicity, and melting points. Pharmaceutical solid polymorphism, for example, has received much attention recently. Its impact on product quality and performance has been discussed

in recent review articles (10–11). Chemical properties include pKa, chemical stability in solid state and in solution as well as photolytic and oxidative stability while biological properties include partition coefficient, membrane permeability, and/or oral bioavailability. Biopharmaceutical properties should be assessed for every form for which there is an interest in development and every form that can potentially be created during processing (e.g., hydrates, anhydrates) or in vivo (e.g., less soluble salts, polymorphic forms, hydrates). The investigation of these properties is termed preformulation in pharmaceutical science. The goal of preformulation studies is to determine the appropriate salt and polymorphic form of drug substance, evaluate and understand its critical proper-ties, and generate a thorough understanding of the material's stability under various processing and in vivo conditions, leading to an optimal drug delivery system. Pharmaceutical preformulation studies need to be conducted routinely to appropriately align dosage form components and processing with drug substance and performance criteria.

Biopharmaceutical assessment provides the information needed to select a solid form, to evaluate the developability of a drug candidate, and to determine its classification according to the Biopharmaceutics Classification System (BCS) (12). The BCS is a scientific framework for classifying a drug substance based on its aqueous solubility, dose, and intestinal permeability (13,14). The BCS guidance is generally considered to be conservative with respect to the class boundaries of solubility, permeability, and the dissolution criteria. Thus, the possibility of modification of these boundaries and criteria has received increasing attention (13,14).

Process Design and Development

Strictly speaking, process and product design and development cannot be separated since a formulation cannot become a product without a process. A formulation without a process is, for example, a pile of powder (K. Morris, 2005, personal communication). Process design is the initial stage of process development where an outline of the commercial manufacturing processes is identified on paper, including the intended scales of manufacturing. This should include all the factors that need to be considered for the design of the process, including facility, equipment, material transfer, and manufacturing variables. Other factors to consider for process design are the target product quality profiles. Depending upon the product being developed, type of process, and process knowledge the development scientists have, it may be necessary to conduct preliminary feasibility studies before completing the process design and development.

The selection of type of process depends upon the product design and the properties of the materials. For example, tablet manufacturing typically involves one of two methods: direct compression or granulation. Direct compression is the most straightforward, easiest to control, and least expensive tablet manufacturing process. It uses two primary unit operations, mixing and compression, to produce the finished tablet. Direct compression is used when ingredients can be blended, positioned onto a tablet press, and made into a high quality tablet without any of the ingredients having to be changed (15). When powders are very fine, fluffy, will not stay blended, or will not compress, then they may be granulated. Granulation is the process of collecting particles together by creating bonds between them. Bonds are formed by compression or by using a binding agent. Wet granulation, the process of adding a liquid solution to powders, is one of the most common ways to granulate. The dry granulation process is used to form granules without using a liquid solution. Forming granules without moisture requires compacting and densifying the powders. Dry granulation can be conducted on a tablet press using slugging tooling, or more typically on a roller compactor.

Pharmaceutical development scientists have just begun making use of computer-aided process design (CAPD) and process simulation to support process development and optimization of manufacturing (16, 39-53). Process simulation has been successfully used in the chemical and oil industries since the early 1960s to expedite development and optimize the design and operation of integrated processes. Similar benefits can be expected from the application of CAPD and simulation in the pharmaceutical industries. Currently, CAPD and process simulation are largely used in drug substance manufacturing. The utility of CAPD and process simulation in drug product design is limited. This is largely because the pharmaceutical industry has traditionally put

emphasis on new drug discovery and development, and the complexity of drug product manufacturing operations are not well recognized. With the emphasis of QbD by the FDA and industry and drug product cost pressures, this trend is expected to change. The use of CAPD and process simulation should result in more robust processes developed faster and at a lower cost, resulting in higher quality products.

Identify Critical Quality Attributes, Process Parameters, and Sources of Variability

A pharmaceutical manufacturing process is usually comprised of a series of unit operations to produce the desired product. A unit operation is a discrete activity that involves physical changes, such as mixing, milling, granulation, drying, compaction, and coating. A physical, chemical or microbiological property or characteristic of an input or output material is defined as an attribute. Process parameters include the type of equipment and equipment settings, batch size, operating conditions (e.g., time, temperature, pressure, pH, and speed), and environmental conditions such as moisture. The quality and quantity of drug substance and excipients are considered as attributes of raw materials.

During process development, raw materials, process parameters and quality attributes[1] are investigated. The purpose of these studies is to determine the critical raw material attributes, process parameters and quality attributes for each process, and to establish any possible relationships among them. Critical quality attributes (CQA) are physical, chemical, biological, or microbiological property or characteristic that must be controlled directly or indirectly to ensure the quality of the product. Critical process parameters (CPP) are process inputs that have a direct and significant influence on critical quality attributes when they are varied within regular operation range. Table II (G. E. Amidon, 2006, personal communication. 2006) lists typical tablet manufacturing unit operations, process parameters, and quality attributes for solid dosage forms. It should be noted that the equipment maintenance, operator training, standard of operation (SOP) related to the specific product manufacturing, and facility supporting systems may link to product quality directly or indirectly. Therefore, risk assessment should be used to reduce variables to be investigated.

Process robustness is defined as the ability of a process to demonstrate acceptable quality and performance and tolerate variability in inputs at the same time. In process robustness studies, effects of variations in process parameters for a candidate process are evaluated. The analysis of these experiments identifies critical process parameters that could potentially affect product quality or performance, and establishes limits for the critical process parameters within which the quality of drug product is assured. Ideally, data used to identify process parameters should be derived from commercial scale processes to avoid any potential impact of scale-up. However, in reality, these studies are often conducted on laboratory or pilot-scale batches. If results from the small-scale batches have not been shown to be size independent, any conclusion from small scale studies may need to be verified in the actual commercial production batches. At the end, the effect of raw material attributes and critical process parameters on product quality or product variability is fully understood and established. Ideally, the interactions between materials attributes and critical process parameters should be understood so that critical process parameters can be varied to compensate for changes in raw materials.

Table II. Typical Unit Operations, Process Parameters, and Quality Attributes for Tableting[a]

Pharmaceutical Unit Operation	Example Process Parameter	Potential Quality Attributes
Mixing	Type and geometry of mixer	Blend uniformity
	Order of addition	Particle size distribution
	Mixer load level	Bulk/tapped density
	Number of rotations (time and speed)	Moisture content
	Agitating bar (on/off pattern)	Flow properties
Milling	Impact/cutting/screening mills	Particle size
	Mill type	Particle size distribution
	Speed	Particle shape
	Blade configuration and type	Bulk/tapped density
	Screen size and type	Flow properties
	Feeding rate	Polymorphic form
	Fluid energy mill	
	Number of grinding nozzles	
	Feed rate	
	Nozzle pressure	
	Classifier	
Wet Granulation	High shear granulation	Power consumption (process control)
	Pre-binder addition mix time	Blend uniformity
	Impeller speed, configuration, and location	Flow
	Chopper speed, configuration	Moisture content
	Spray nozzle type and location	Particle size and distribution
	Method of binder addition	Granule size and distribution
	Binder fluid temperature	Granule strength and uniformity
	Binder addition rate and time	Solid form
	Post-granulation mix time	
	Bowel temperature	
	Fluid bed granulations	
	Mixing time	
	Spray nozzle (type/quantity/ pattern/configuration)	
	Method of binder addition	
	Binder fluid temperature	
	Binder fluid addition rate and time	
	Inlet air flow rate, volume, temperature, and dew point	
	Exhaust air temperature, flow	
	Filter properties and size	
	Shaking intervals	
	Product temperature	
Drying	Fluidized bed	Granule size and distribution
	Inlet air volume, temperature, dew point	Granule strength, and uniformity
	Exhaust air temperature, flow	Particle size
	Filter properties	Flow
	Shaking intervals	Bulk/tapped density
	Product temperature	Moisture content
	Total drying time	Residual solvents
	Tray	
	Quantity carts and trays per chamber	
	Quantity of product per tray	
	Drying time and temperature	
	Air flow	
	Inlet dew point	
	Vacuum/microwave	
	Jacket temperature	
	Condenser temperature	
	Impeller speed	
	Vacuum strength	
	Microwave potency	
	Electric field	
	Energy supplied	
	Product temperature	
Roller compaction	Roll speed	Appearance
	Gap setting	Ribbon/particle size and shape
	Roll pressure	Ribbon density, strength, and thickness

Table II. Continued

Pharmaceutical Unit Operation	Example process parameter	Potential Quality Attributes
	Auger screw rate	Solid form
	Roller type	
Compaction[b]	Compression speed and force	Target weight
	Pre-compression force	Weight uniformity
	Feed frame type and speed	Content uniformity
	Hopper design, height, and vibration	Hardness
	Tablet weight and thickness	Thickness
	Depth of fill	Tablet porosity
	Punch penetration depth	Friability
		Visual attributes
		Moisture content
Coating[b] Fluid bed, Pan	Product temperature	Weight of core tablets
	Total pre-heating time	Appearance
	Spray nozzle (type/quantity/ pattern/configuration)	Visual attributes
	Individual gun spray rate	% Weight gain
	Total spray rate	Film thickness
	Pan rotation speed	Color uniformity
	Atomization air pressure	Hardness
	Pattern air pressure	Thickness
	Inlet air flow, temperature, dew point	Friability
	Exhaust air temperature, air flow	
	Product temperature	
	Total coating time	

Control Manufacturing Processes to Produce Consistent Quality over Time

Under the QbD for generic drugs, the effects of raw materials including both drug substance and excipients, and process parameters on the product quality are well under-stood. This means that manufacturers have knowledge of the operating range as well as the proven range of critical raw material attributes and process parameters. The operating range is defined as the upper and/or lower limits for raw material attributes and process parameter values between which the attribute and parameter are routinely controlled during production in order to assure reproducibility. The proven range is defined as the upper and/or lower limits for process parameter values between which the parameter is known to produce a high quality product that delivers the therapeutic benefit claimed on the label. The proven range can be established based on historical and/or experimental data. It can also be established based on scientific and operational judgment and expertise.

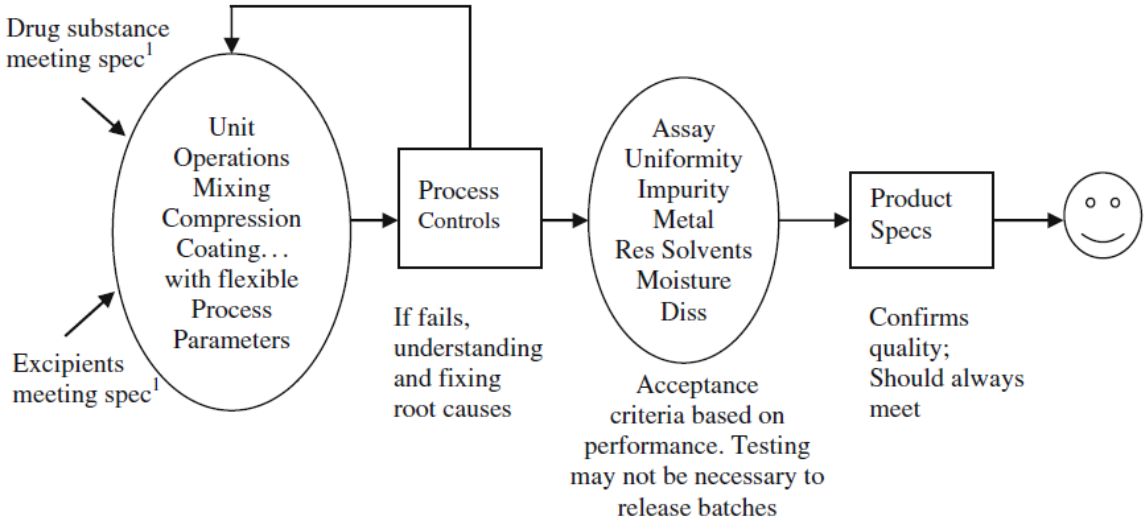
Within the QbD, design space is defined as the multi dimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide quality assurance (3). Working within the FDA approved design space is not considered a change. Movement out of the design space 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. At an October 2006 Advisory Committee for Pharmaceutical Science meeting, the following issues were raised on design space:

– How were design space and control space established for each unit operation?

– Is the design space for each unit operation independent of equipment design and batch size?

– How does control space relate to design space?

– How does control space relate to operational ranges in the Master Batch Record?



A simplified quality assurance diagram under the QbD for generic drugs.

2. Seven steps of quality by design start up plan [2]

1. Hire an independent Quality by design expert.
2. Audit your organization and process with the expert conducting a gape analysis.
3. Hold a basic quality by design workshop with all your personal.
4. Review the expert's report and recommendation.
5. Draft an implementation plan, timelines and estimated costs.
6. Assign the resources (or contract out).
7. Retain the independent expert as your "Project Assurance" advisor.

3. Primary QbD Documents [4]

3.1 Risk Assessment Report(s)

1. Performed throughout QbD Process
2. Particularly important to process development

3.2 Quality Target Product Profile (QTPP)

1. Defines the desired product characteristics and sets development goals.

3.3 Control Strategy Summary

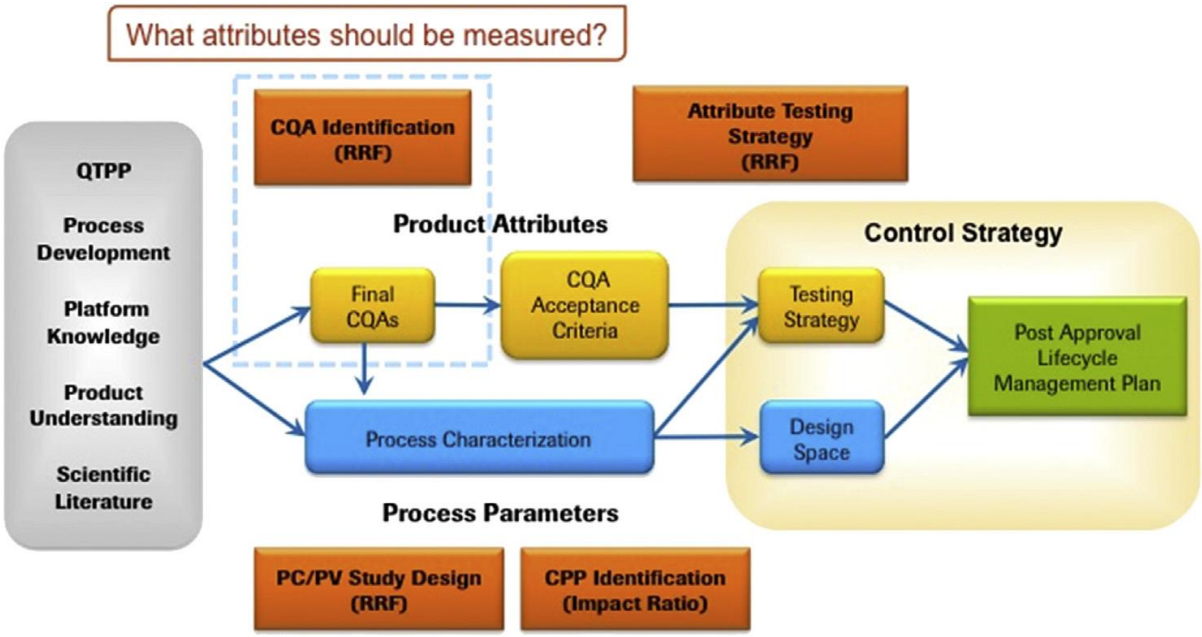
1. Defines the process, its inputs and outputs, and how it is controlled.

3.4 PPQ Report(s)

1. Formal verification that the process Control Strategy has been defined appropriately and repeatedly produces the desired results.

3.5 Continued Process Verification (CPV) Reports

1. Assuring that during routine commercial production, the process remains in a state of control (FDA); involves feedback loops into the QbD "process" where intentional process changes and/or observed variability is assessed for risk, characterized, re-validated, etc.



As defined by an FDA official(Woodcock, 2004), the QbD concept represents product and process Performance characteristics scientifically designed to meet specific objectives, not merely empirically derived from performance of test batches. Another FDA representative (Shah, 2009) states that introduction of the QbD concept can lead to cost savings and efficiency improvements for both industry and regulators. QbD can facilitate innovation, increase manufacturing efficiency, reduce cost/product rejects, minimize/eliminate Potential compliance actions, enhance opportunities for first cycle approval, streamline post approval changes and regulatory processes, enable more focused inspections, and provide opportunities for continual improvement (Shah, 2009).[3]

4. ICH Q8 guideline:

Quality- by-design (QbD) is a concept introduced by the International Conference on Harmonization (ICH) Q8 guideline, as a systematic approach to development, which begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. Predefined objectives make up the quality target product profile (QTPP), that is, the summary of the drug product quality characteristics that ideally should be achieved.

The ICH Q8 guideline on scientifically based pharmaceutical development serves to provide opportunities for pharmaceutical manufacturers to seek regulatory flexibility and mitigation of some activities required for product registration and/or subsequent post approval change process. The ICH Q8 guideline describes good practices for pharmaceutical product development.

The ICH Q8 guideline suggests that those aspects of drug substances, excipients, container closure systems, and manufacturing processes that are critical to product quality should be determined and control strategies justified.[3]

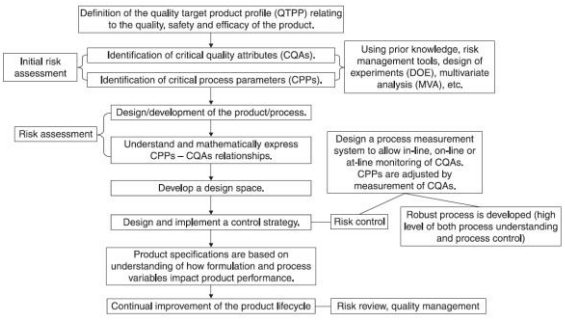
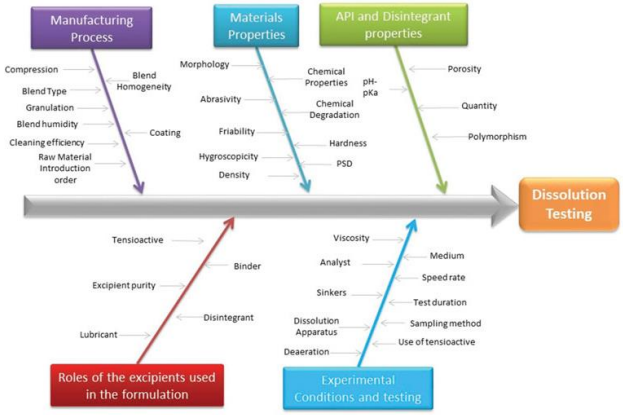
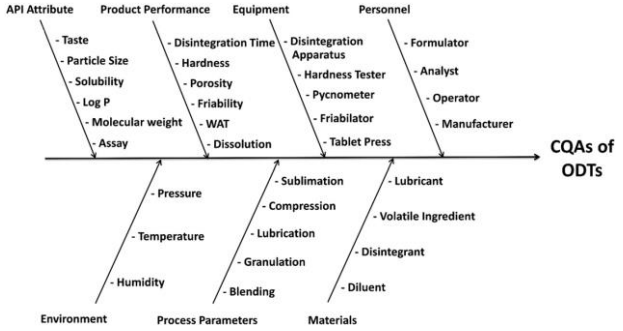


Fig: QbD approach, combining design space development and risk management tools

5. Ishikawa diagram:



Fishbone Diagram of the factors thought to influence product CQAs.[17]



Ishikawa fishbone diagram depicting effect of potential factors on CQAs of Orally disintegrating tablets [18]

6. Applications of quality by design:

S.no	Application	Reference Article
1.	Application of Quality by Design to optimize a stability indicating LC method for the determination of ticagrelor and its impurities	19
2.	Application of the Quality by Design Approach to the Freezing Step of Freeze-Drying: Building the Design Space	20
3.	Application of quality by design elements for the development and optimization of an analytical method for protamine sulfate	21
4.	Application of Quality by Design principles in the development and evaluation of semisolid drug carrier systems for the transdermal delivery of lidocaine	22
5.	Application of Quality by Design Concepts in the Development of Fluidized Bed Granulation and Tableting Processes	23
6.	UHPLC method for multiproduct pharmaceutical analysis by Quality-by-Design	24
7.	Application of quality by design concept to develop a dual gradient elution stability indicating method for cloxacillin forced degradation studies using combined mixture process variable models	25
8.	A Quality by design (QbD) approach on starch-based nanocapsules: A promising platform for topical drug delivery	26
9.	Application of a Quality by Design Approach to the Cell Culture Process of Monoclonal Antibody Production, Resulting in the Establishment of a Design Space	27
10.	Quality by Design approach in the development of an ultra-high-performance liquid chromatography method for Bexsero Meningococcal Group B Vaccine	28
11.	Application of Quality by Design to the characterization of the cell culture process of an Fc-Fusion protein	29
12.	Application of quality by design approach for intranasal delivery of rivastigmine loaded solid lipid nanoparticles: Effect on formulation and characterization parameters	30

13.	Retrospective Quality by Design (rQbD) applied to the optimization of orodispersible films	31
14	Application of Analytical Quality by Design concept for bilastine and its degradation impurities determination by hydrophilic interaction liquid chromatographic method	32
15	Application of quality by design to formulation and processing of protein liposomes	33
16	Application of Analytical Quality by Design principles for the determination of alkyl p-toluenesulfonates impurities in Aprepitant by HPLC. Validation using total-error concept	34
17	Applications of quality by design (QbD) and its tools in drug delivery	35
18	A quality by design approach using artificial intelligence techniques to control the critical quality attributes of ramipril tablets manufactured by wet granulation	36
19	Quality by design (QbD) approach for design and development of drug-device combination products: A case study on flunisolide nasal spray	37
20	Quality by design approach in the optimization of the spray-drying process	38

7. CONCLUSION:

The basic conclusion behind QbD is to apply quality standards for development efforts and develop a robust and reliable method with a degree of assurance that process being followed and product being manufactured is according to mentioned specification. QbD has wide variety of application from evaluation to development. Knowledge of ICH guidelines Q8,Q9,Q10 is prime importance in order to study QbD. QbD is cost and time efficient approach in design and manufacturing with DoE, risk assessment, and PAT and its tools to achieve better understanding of material and process which make QbD available and feasible to pharmaceutical field. The main reason to implement QbD in industry is regulatory requirements rules and protocols. QbD replaces prior used frizzed approach of process development by providing a design space concept. QbD will become a necessity, therefore all stakeholders should adapt to its implementation.

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