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Articulation of Quality By Design Elements for Product Development and its Unique Applications

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ABSTRACT

Quality by Design (QbD) is a methodical approach to pharmaceutical product development that begins with predefined objectives and emphasizes product and process comprehension and process control based on sound science and quality risk management. Pharmaceutical development should lead to the design a quality product and its manufacturing process to meet the QTPP and CQA parameters. To arrive at the robust product development QbD articulation is important which is missing in most of the reviews. This review articulates the QbD elements in the product development. QbD process stars with identification of QTPP and source CQA from QTPP. CMAs and CPPs are derived with risk assessment from the product ingredients and process. Their impact on the CQAs can be studies with DoE tools. The information and knowledge gained from pharmaceutical development studies and manufacturing experience provide scientific understanding to support the design space and control strategy. Product process follows life cycle management approach with continuous improvement. PAT tools are utilized for the online monitoring of the processes. This review paper is dedicated to provide QbD element articulation in product development and its unique applications in the various areas of the product development such as Biotechnology, Nanotechnology products, Nasal products, Inhalation, Injectable products, Targeted drug delivery, complex Solid oral, Transdermal and topical products, Bioavailability and dissolution enhancement, Analytical processes and API manufacturing etc. Current trends in the technical application of the PAT tools are discussed.

Keywords: Quality by Design (QbD), Quality Target Product Profile (QTPP), Critical Quality Attributes (CQA) and Design of Experiment (DoE): Product development application of QbD

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Introduction

Quality by Design (QbD) has supported both industry and FDA to achieve scientific, risk based, and proactive approach to pharmaceutical product development. [1] The QbD is a systemic approach to pharmaceutical product development which leads to formulations and manufacturing processes with desired quality attributes. [2] Pharmaceutical QbD may include achieving meaningful control strategy that are based on clinical performance to increase process capability by enhancing product and process design. [3] The theme of QbD is Quality can't be tested into the product, but it should be built into it. [4]

Studies have shown that the Lifecycle management approach for the product development supports establishment of the design space and working within design space is not considered as change by the regulatory agencies. [5] The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines ICH Q8 (Pharmaceutical Development), ICH Q9 (Quality Risk Management) and ICH Q10 (Pharmaceutical Quality Systems) are basis for the QbD in product development to achieve the quality product. [6] Prime requirement for the QbD implementation are to establish relationship of the product CQAs with CMAs and CPPs. [7] QbD reduces post approval regulatory submissions with design space development and facilitates novel approaches to process validation which is continuous process improvement and lifecycle management. [8]

Most of the review articles presented partial elements of QbD and articulation is missing for the application. This review article focuses on the QbD elements articulation along with supporting elements to achieve the quality products with design space. Current trends in the PAT applications are described along with unique application of QbD in product development.

Elements of Quality by Design (QbD)

QbD encompasses following listed elements of pharmaceutical development. These elements will lead to the product with intended performance characteristics. Pharmaceutical development will provide a complete understanding of the product and its manufacturing process by application of QbD elements. [9]

- Quality target product profile (QTPP)
- Critical quality attributes (CQAs)
- Critical material attributes (CMAs)
- Critical process parameters (CPPs)
- Control strategy
- Product Lifecycle Management and Continual Improvement

  Supporting elements including

- Risk assessment
- Design of Experiment (DoE)
- Process Analytical Technologies (PAT)

These elements are described in the following sections along with their articulation in product development.

Quality Target Product Profile (QTPP)

QTPP identification is the starting point for the product development. The US Food and Drug Administration (FDA) QbD initiative provides an enhanced assessment approach by introducing the concept of a QTPP. [10] QTPP is defined as, "A prospective summary of the quality characteristics of drug product that ideally will be achieved to ensure the desired quality, taking in to account safety & efficacy of drug product." QTPP is not specification because it includes tests such as bioequivalence or stability that are not carried out in batch to batch release. Based on the clinical and pharmacokinetic characteristics as well as the in vitro dissolution and physicochemical characteristics of the reference product QTPP can be defined for the product. [11, 12] QTPP parameters for example Generic Acetriptan Tablets, 20 mg are presented in the below table 1. [13]

Table 1: Quality Target Product Profile (QTPP) parameters

QTPP Elements		Target	Justification
Dosage form		Tablet	Pharmaceutical equivalence requirement: same dosage form
Dosage design		Immediate release tablet without a score or coating	Immediate release design needed to meet label claims
Route of administration		Oral	Pharmaceutical equivalence requirement: same route of administration
Dosage strength		20 mg	Pharmaceutical equivalence requirement: same strength
Pharmacokinetics		Immediate release enabling T_{max} in 2.5 hours or less; Bioequivalent to RLD	Bioequivalence requirement Needed to ensure rapid onset and efficacy
Stability		At least 24-month shelf-life at room temperature	Equivalent to or better than RLD shelf-life
Drug product quality attributes	Physical Attributes	Pharmaceutical equivalence requirement: Must meet the same compendial or other applicable (quality) standards (i.e., identity, assay, purity, and quality).	
	Identification		
	Assay		
	Content Uniformity		
	Dissolution		
	Degradation Products		
	Residual Solvents		
	Water Content		
	Microbial Limits		
Container closure system		Container closure system qualified as suitable for this drug product	Needed to achieve the target shelf-life and to ensure tablet integrity during shipping
Administration/Concurrence with labeling		Similar food effect as RLD	RLD labeling indicates that a high fat meal increases the AUC and C_{max} by 8-12%. The product can be taken without regard to food.
Alternative methods of administration		None	None are listed in the RLD label.

Originator's product characteristic will be strictly used for defining the QTPP for the Biosimilar products. [14] Sterile Product QTPP may be unique in terms of need for administration devices and requirements specific to sterile products such as endotoxin limits. [15]

QTPP identification will be followed by CQAs identification based on the risk assessment. CQAs will be derived from the QTPP considering impact on the safety of the patients.

Critical Quality Attributes (CQAs)

A Critical quality attribute (CQA) is "A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality." CMAs and CPPs are identified during product development and are linked to the CQAs. Risk assessment process will be used to facilitate this evaluation. CQAs include but are not limited to Assay, Dissolution, Sterility, Degradation products and Crystallinity etc. [16, 17] Active Pharmaceutical Ingredient CQAs can also be controlled with QbD. [18]

Identification of the CQAs is followed by risk assessment of Active pharmaceutical ingredient and Formulation variables to arrive at the CMAs.

Critical Material Attributes (CMAs)

CMAs includes physical, chemical, biological, or microbiological properties or characteristics of an input material used in the product development. CMAs should be within an appropriate limit to ensure the desired quality of that drug substance, excipient or in-process material. Risk assessment process is used to derive the CMAs. [19, 20]

Identification of the CMAs is followed by identification of the CPPs of the process used for the product manufacture with use of the risk assessment tools.

Critical process parameters (CPPs)

A process parameter is critical when a realistic change in that parameter can cause the product to fail to meet the QTPP. For example if development studies showed that the granulation was affected by realistic changes in impeller speed or granulation time then these should be identified as CPPs. Risk assessment process can lead to identification of the CPPs. Control strategies should be defined for the identified CPPs. CPPs are studied for their impact on the CQAs. Critical parameters of process and materials and their link with the product CQAs is presented in the following figure 1. [21, 22]

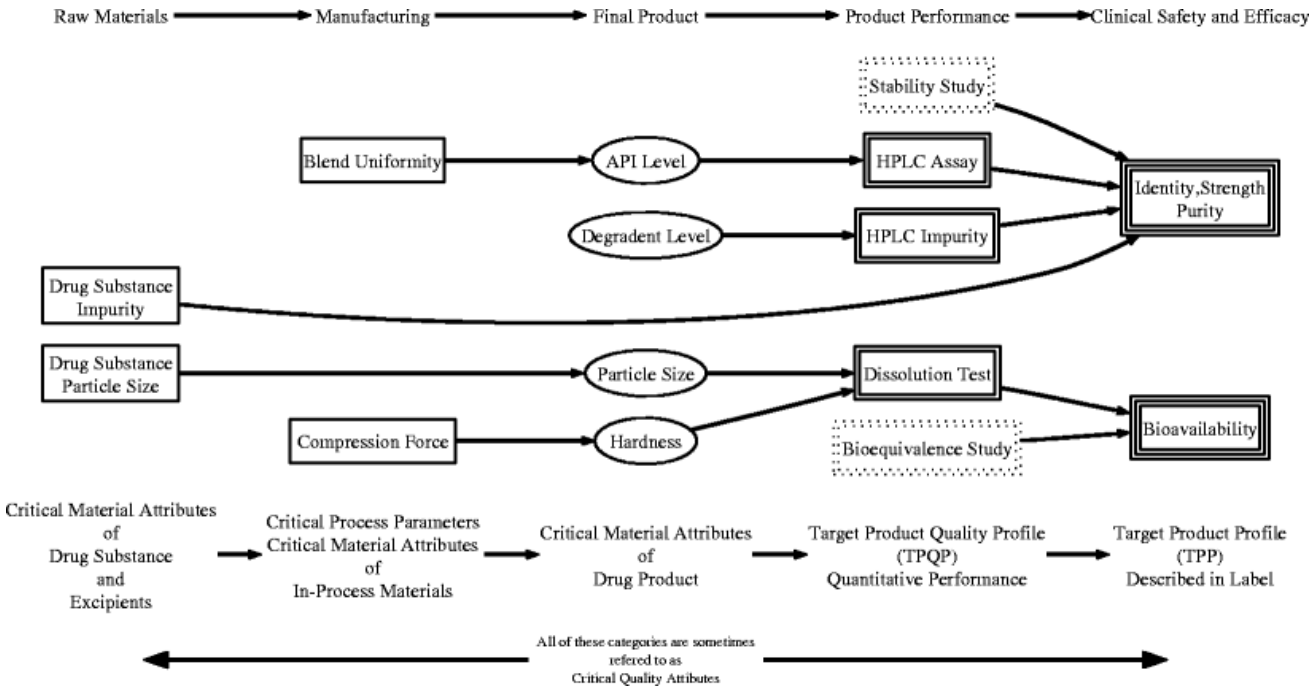

Figure 1: Critical parameters of process and materials with their link to CQAs

Resources can be utilized in the most critical areas with QbD process. Dossier with QbD compliant product development help FDA reviews decrease post-approval regulatory submissions required to make process changes. [23] Process modeling tools such as PAT can play a role in developing robust and economically efficient manufacturing processes. [24]

Based on the knowledge of the CMAs and CPPs and their link to the CQAs robust process development will be carried out. Formulation development trials at lab will be scaled to the Pilot or Production scale and Control strategies will be derived. DoE can be used for the experimentation of the CPPs and CMAs to study their impact on the CQAs to derive the design space.

Control Strategy

Control strategy is defined as "a planned set of controls, derived from current product and process understanding that assures process performance and product quality". Risk assessment is used to derive the Control strategy for the CQAs. The control strategy is derived for the procedural controls, in-process controls, lot release testing, process monitoring, characterization testing, comparability and stability testing. [25] A control strategy may include design spaces and final product specifications. Control strategy for the commercial scale will be proposed in the submission to FDA. [26]

Design space is designed for the product which will be verified by the regulatory agency. The Design Space encompasses the proven acceptable ranges for CMAs, CPPs and CQAs. Normal operating ranges are a part of the design space [27]. Risk assessment, experimental design along with the use of literature / prior experience can be leveraged to derive the design space for the product. [28] Material attribute design space is independent of scale and configuration of process equipment and the related process variables. Thus

post-approval changes of equipment scale, nameplate, or location would not require any regulatory approval. [29]

Product submission will include the proposed product commercialization design space with QbD Product life cycle and continual improvement approach.

Product Lifecycle Management and Continual Improvement

Risk assessment throughout product development leads to robust product with less deviations. [30] Manufacturing process performance will be monitored to confirm that it is working within design space. Process capability and trend analysis will be performed. Continual improvement of the drug product will be performed with knowledge gained from the product. [31]

Supporting elements to achieve the product development with QbD application are Risk assessment, DoE and PAT. These tools are discussed in the following sections. These are integral part of the QbD.

Risk assessment

QRM principles are used to achieve the enhanced knowledge of the product. [32] Commonly used tools are Ishikawa diagram & Failure Mode and Effects Analysis (FMEA). [33] QRM helps in identifying effect of CMAs and CPPs on CQAs. This risk assessment helps regulators to achieve the greater understanding of the product and leads to patient benefits. [34]

Risk assessment of the drug substance attributes performed to evaluate the impact that each attribute could have on the drug product CQAs. The outcome of the assessment and the accompanying justification is provided as a summary in the Pharmaceutical development report. The relative risk that each attribute presents was ranked as high, medium or low. The high risk attributes warranted further investigation whereas the low risk attributes required no further investigation. The medium risk is considered acceptable based on current knowledge. Further investigation for medium risk may be needed in order to reduce the risk. [35] Following figure 2 shows overview of a typical QRM process. [36, 37]

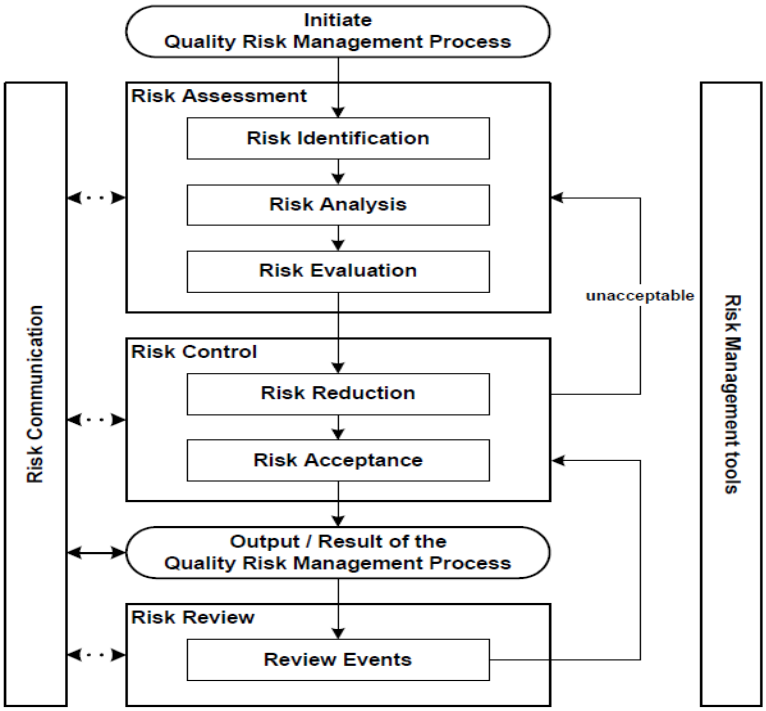

Figure 2: Overview of a typical QRM process

QRM process described above could help the oral Peptide delivery system development which has many formulation barriers. QRM helps to manage on the resources (human, financial & time) related to the final product quality in more productive way. [38]

Identified CMAs and CPPs can be studied with DoE tools for their impact on CQAs to achieve design space.

Design of Experiments (DoE)

DoE process is used for the attribute interaction studies. Studies on CPPs and CMAs for their impact on the CQAs can be carried out with DoE to arrive the design space. This will lead to the product meeting CQAs and QTPP. [39] DoE studies can be carried out at lab scale or on pilot scale processes. [40] Legacy drug products are developed with application of Multivariate statistical analysis and DoE to achieve design space. [41] QbD, PAT, real-time data generation and control monitoring systems knowledge will be better captured, managed and shared during product life cycle for product continuous improvements. [42]

Process Analytical Technology (PAT)

PAT tool can be used for the product development from early development to commercialization. FDA PAT Guidance and ICH Q8 suggest for the PAT tool utilization to monitor process online. [43, 44] PAT tools are classified as Multivariate Tools for Design, data acquisition and analysis, process analyzers, process control and continuous improvement and knowledge management. [45, 46] Current trends in the PAT tools application are described for product development.

NIR spectroscopy is used in coating process, [47] Determination of content uniformity, compression force and crushing strength for Orbifloxacin tablets, Film coat curing and release monitoring, [48, 49, 50] Monitoring blend potency and uniformity in the manufacturing of an oral solid dosage product. [51] PAT tools used for process monitoring and control tools that enables monitoring of real-time release. [52] Confocal Raman microscopy to study content uniformity and the polymorphic form of a drug substance distributed within a lipid based inhalable powder. [53] Additional application of NIR can include for design and scale-up of a batch mixing process, [54] Coating thickness monitoring for its impact on dissolution. [55] Thus PAT can support for QRM to arrive at design space. [56]

This discussion summarizes the articulation of the QbD elements in the product development. QbD process stars with QTPP and CQA identification. CMAs and CPPs are derived with risk assessment from the product understanding. Their impact on the CQAs can be studies with DoE tools. This will lead to identification of the control strategy and design space. Product process will be follow life cycle management approach with continuous improvement. PAT tools are utilized for the online monitoring of the processes. All this lead to robust product development.

Following literature reports of unique applications of QbD elements in different areas of Formulation development are summarized.

Biotechnology

Protein Liposomes

Xu X et al. prepared Superoxide dismutase containing liposome formulations using freeze and thaw unilamellar vesicles followed by use of risk analysis and D-optimal statistical design resulting in liposomes with 6 months stability in aqueous dispersion state at 4 °C. [57]

Monoclonal Antibody Product

Nagashima H et al. used QbD for cell culture process of monoclonal antibody production resulting in the establishment of a design space with QRM. [58]

Peptide Product

Reihaneh Manteghi et al. prepared antimicrobial peptide modification and formulation design analyzed the potential risks in the antimicrobial Peptide PEGylation process. [59]

Biosimilar product

Rathore AS et al. studied development of a purification process for the production of a biosimilar product granulocyte colony-stimulating factor (GCSF) using QbD. [60]

Topical Formulations

Marto J et al. prepared starch based Nanocapsules formulation of lipophilic bioactive molecule for topical drug delivery and studies indicated a good physical stability, safety and cosmeticity. [61]

Creams

Mendonsa NS et al. formulated topical creams of Hydrocortisone acetate via hot melt extrusion technology coupled with a DoE approach to derive ideal product properties. [62]

Transdermal products

Nanostructured lipid carriers

Qian Kang et al. formulated and optimized Tripterine loaded in Nanostructured lipid carriers (NLCs) for transdermal delivery with emulsification evaporation method. Different drug administration methods and dermatokinetic study revealed the rapid lose water of gel could enhance NLCs into deep skin layer. [63]

Transferosomes

Fernández-García R et al. prepared Transferosomes as nanocarriers gel have shown promising results in the alleviation of symptons in orthreothritis with non-severe skin and subcutaneous tissue disorders. [64]

Ethosomes

Jain S et al. formulated ethosome of Diclofenac for enhanced anti-inflammatory activity using 4 × 5 full-factorial design with Phosphatidylcholine & Cholesterol and studied skin permeation kinetics. [65]

Nanotechnology based products

Nanoparticles

Park SY et al. formulated Sorafenib loaded Nanoparticles with Fat and supercritical fluid (NUFS™) to improve oral bioavailability and In vivo pharmacokinetics studies in beagle dogs demonstrated that optimized formulation of Sorafenib exhibited higher blood drug profiles indicating better absorption compared to the reference tablet (Nexavar®). [66]

Yerlikaya F et al. developed and characterized Paclitaxel Nanoparticles with Ishikawa diagram risk assessment and screened by Plackett Burman design and finally Nanoparticles were optimized using Box Behnken design. In vitro cytotoxicity test showed that the developed Nanoparticles are more efficient than free Paclitaxel in terms of antitumor activity. [67]

Nanostructured lipid carrier

Gurumukhi VC et al. fabricated Nanostructured lipid carrier (NLC) encapsulating Efavirenz explored characterizations and in vivo safety resulting high drug encapsulated potential nanocarrier to enhance bioavailability and confirms safety with promising acceptable criteria. [68]

Nanoliposomes

Mahtab A et al. formulated Teriflunomide loaded Nanoliposomes prepared with Thin-film hydration technique for treatment of Rheumatoid arthritis. In vivo pharmacokinetic study results revealed sustained release profile with higher therapeutic efficacy of the drug at the inflammatory site compared with Teriflunomide solution. [69]

Nanosuspension

Verma S et al. studied process of Nanosuspension preparation with Multiple linear regression analysis and ANOVA to create design space and designed model the process of Microfluidization for predictive purposes. [70]

Nanoemulsion

Negi P et al. formulated biocompatible Lidocaine and Prilocaine loaded Nanoemulsion system for enhanced percutaneous absorption and superior permeation rates with higher concentrations of the drugs in skin layers from the optimised formulations when compared to marketed cream. [71]

Inhalation products

Microparticles

Zhang L et al. optimized Budesonide loaded large porous Microparticles for Inhalation drug delivery. [72]

Dry powder inhalers

Buttini F et al. studies development of Dry powder inhalers with QbD framework. [73]

Nasal Products

Bartos C et al. formulated Levodopa containing Dry powder for Nasal delivery. Based on risk assessment, Levodopa and Chitosan or Sodium hyaluronate as mucoadhesive matrix formers were co-milled using planetary ball mill to prepare Microparticles as drug delivery systems. [74]

Injectable Formulations

Lipid injectable emulsion

Deng Y et al. prepared fat soluble vitamins Lipid injectable emulsion & design space was obtained with DoE. Safety of the optimal emulsion was evaluated as acceptable through the determination of lysophospholipid content and an in vitro hemolysis assay. [75]

Lyophilized liposomes

Porfire A et al. developed lyophilized Liposomes with Simvastatin to increase shelf-life of Liposomes with Design space. [76]

Self Nanoemulsified Drug Delivery System (SNEDDS)

Zidan AS et al. studied product variability of a SNEDDS of Cyclosporine A & demonstrated the ability to understand the impact of nanodroplets size on the SNEDDS variability (Size) by different product analyzing tools such as Near Infrared (NIR) and Chemometric analysis. [77]

Targeted Drug Delivery

Microspheres for colon-specific delivery

Hales D et al. formulated Enoxaparin sodium loaded polymeric Microspheres for colon-specific delivery then CPPs and CQAs were identified and achieved design space. [78]

Bone targeting therapeutic Radiopharmaceutical

Lange R et al. prepared small scale process for Rhenium 188 HEDP which is a therapeutic Radiopharmaceutical for treatment of Osteoblastic bone metastases for bone targeting. The effect of CPPs on product quality and stability of 188Re-HEDP was studies. [79]

Limicubes

Javed MN et al. developed and optimized Bicontinuous cuboidal shaped Mucoadhesive Microcrystalline delivery systems (Limicubes) for oral delivery of Rosuvastatin. [80]

Solid Oral products

Bilayer combination tablet

Ah Ram Lee et al. optimized formulation of a bilayer combination tablet Telmisartan and Amlodipine besylate (Telmiduo®) manufactured via high shear wet granulation and showed greater physical stability along with in-vivo equivalence. [81]

Controlled Release product

Saurí J et al. studied physicochemical phenomena involved in Controlled release of Captopril matrix tablets with DoE. [82]

Pellets

Wang J et al. developed Naproxen loaded core pellets for Colon specific pellets and used Plackett Burman design to screen potential high risk factors. [83]

Fluid bed granulation

Lourenço V et al. studied industrial Pharmaceutical fluid bed granulation with QbD.[84]

Spray drying

Baldinger A et al. optimized Spray drying process with DoE. Non-invasive NIR measurement was used for correlating the CQA particle size with size determined by laser diffraction. [85]

Roller Compaction

Hsu SH et al. studied modeling and control of Roller compaction for pharmaceutical manufacturing with DoE. [86]

High drug load tablet

Sun CC et al. developed high drug load tablet formulation based on assessment of powder manufacturability for novel drug AMG458. [87]

Tablet with artificial intelligence

Aksu B et al. applied Artificial intelligence techniques to control the CQAs of Ramipril tablets manufactured by wet granulation and design space was derived using DoE with Artificial neural networks (ANNs). [88]

Bioavailability Enhancement

Chauhan MK et al. performed bioavailability enhancement of Polymyxin B with novel drug delivery Niosomes as carrier system. Formulation showed promising results in vitro antifungal, rat creatinine and cytotoxicity assay. [89]

Dissolution Enhancement

Parmar K et al. improved dissolution properties of poorly water soluble herbal active ingredient Embelin by formulating Liquisolid systems and optimized formulation with DoE. [90]

Scale up

Coating process

Agrawal AM et al. reviewed Scale up of pan coating process with DoE and PAT tool. [91]

Orodispersible films

Bülbül EO et al. showed improvement has been achieved for schizophrenic patients by the production of Quetiapine fumarate loaded Orodispersible films and the process of scale up in films has been demonstrated. [92]

Analytical QbD

UV spectrophotometric method

Kualiti MP et al. developed a robust UV spectrophotometric method for estimation of Vilazodone and showed that Sampling interval and slit width were the two influential Critical method variables which require special attention by the analyst while setting up the method control strategies and future experimentations for continual improvement in method performance. [93]

High Performance liquid chromatography (HPLC)

Moreira CS et al. developed and optimized stability-indicating Chromatographic method for Verapamil hydrochloride and its impurities in Tablets using an Analytical Quality by Design (AQbD) approach. [94]

Ultrafast liquid chromatography

Panda SS et al. studies Ultrafast liquid chromatography for estimation of hallucinogenic agents in drug products, drug in microdialysis samples, and drugs in skin diffusate samples. [95]

Ultrahigh performance liquid chromatography

Alexander H. Schmidt et al. developed a stability indicating UHPLC method for Ebastine in the API and pharmaceutical formulations and established model for Design Space is accurate. [96]

Liquid chromatography-Tandem Mass spectrometry method

Pasquini B et al. developed a Liquid chromatography-Tandem Mass spectrometry method for the determination of Nintedanib and its impurities. Critical method parameters (CMPs) and critical method attributes (CMAs) were studied with DoE. [97]

Tristimulus Colorimetry

Hetrick EM et al. studies on Integrating Tristimulus Colorimetry into pharmaceutical development for color selection and physical appearance with QbD. [98]

Capillary electrophoresis

Orlandini S et al. developed a Capillary electrophoresis method for the analysis of Zolmitriptan and its impurities. DoE study was conducted to achieve the Design space. [99]

Extractables & Leachables Assessment

Jenke D et al. studied Extractables & Leachables assessment & establishing a design space for terminally sterilized aqueous drug products stored in a plastic packaging system. [100]

API manufacture

AM Ende D et al. studied Torcetrapib manufacturing process with application of risk assessment, multivariate design and a proposed criticality assessment all of which coalesce into an design space. [101]

Conclusion

This review articulated the whole QbD process for product development. QbD process starts with QTPP and CQA identification. CMAs and CPPs are derived with risk assessment. Their impact on the CQAs can be studies with DoE tools. The information and knowledge gained from pharmaceutical development studies and manufacturing experience provide scientific understanding to support the design space and control strategy. Product process will be follow life cycle management approach with continuous improvement. PAT tools are utilized for the online monitoring of the processes. Unique applications of QbD in the various areas of the product development such as Biotechnology, Nanotechnology products, Nasal products, Inhalation, Injectable products, Targeted drug delivery, complex Solid oral, Transdermal and topical products, Bioavailability and dissolution enhancement, Analytical processes and API manufacturing etc. are described for easy industrial adoption. PAT tools are becoming increasingly famous for the online testing applications of the product thus current trend applications are described. Outcome of QbD product development will be a robust product development and product submission will lead to the less regulatory post approval queries on the changes during product life cycle management and continuous improvement of the process.

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Authors Contributions

All authors have contributed equally.

Conflict of Interests

Declared none

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