A glance on the history of pharmaceutical quality by design

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Abstract

Introduction

Quality by design is a risk management and science-based approach promoted by the United States Food and Drug Administration to enhance pharmaceutical development throughout a product’s life cycle. Risk assessment approaches, process analytical technology tools and mathematical, statistical and continuous improvement tools are important elements of quality by design continuum, which mainly focus on the identification of critical parameters and defining a design space statistically. In this article, quality by design principles were discussed on the basis of several published case studies including development of bulk powder, granules, capsules, orally dispersible tablets, botanical drug products, nanoparticles and biopharmaceutical drugs. The use of quality by design approach in development of different methods, formulations and systems such as chromatographic and dissolution methods, physiologically absorption models, in situ implant formulations and single-use bioreactors was also considered.

Conclusion

Full adoption of quality by design has great long-term benefits including enhanced understanding, well-defined system and regulatory flexibility. Quality by design has a great application potential for almost every step of pharmaceutical development. Industry, academia and regulatory bodies should cooperate to increase the level of quality by design implementation in the future.

Introduction

Quality by design (QbD) is one arm of the quality system based on building quality in the development phase and throughout a product’s life cycle. It can be underlined with risk management and science together1. International Conference on Harmonisation (ICH) defines QbD as ‘... a systematic approach to pharmaceutical development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.’

In 2002, United States Food and Drug Administration (FDA) made the first steps towards integrating the QbD concept into current good manufacturing practices (cGMPs), and in 2004 FDA released its final report on ‘Pharmaceutical cGMPs for the 21st Century: A Risk Based Approach’ guideline, with the aim of modernising the regulation of pharmaceutical manufacturing and product quality. This pharmaceutical quality paradigm shift is highlighted in the FDA’s ‘Process Analytical Technology (PAT): Guideline for Industry – A Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance’. Besides this, ICH’s current ‘Q8(R2) Pharmaceutical Development’, ‘Q9 Quality Risk Management’ and ‘Q10 Pharmaceutical Quality System Guidelines’ were released in 2009, 2005 and 2008, respectively. QbD was first introduced into the Chemistry, Manufacturing and Controls review process in 2004 as a result of the Pharmaceutical cGMPs for the 21st Century Initiative3.

Despite having been seen as a new paradigm in the pharmaceutical industry, QbD is not that new. In the 1950s, the first thoughts of operational windows, which transformed today’s design space, came up. Joseph M Juran created the QbD as a term in the 1970s and popularised it in the 1990s with several publications. After aforementioned guidelines were released, global regulatory agencies and industry have been trying to understand and to implement the QbD approach to the manufacturing process, for almost a decade. The pharmaceutical industry seems behind the times, but also with the 30–40 years of field experience, learning and implementation phases can be carried out quicker than other industries.4,5

QbD fundamentally means building quality in, not testing it. QbD is good business and good science, with a complete product and process understanding. Compared with traditional quality by the testing (QbT) approach (Figure 1), QbD has great opportunities to build an efficient and flexible system with increased manufacturing efficiency, reduced costs, project rejections and waste. With scientific knowledge and risk management, QbD ensures consistent information and incorporated risk management6. While everyone is aware of these benefits and opportunities, QbD has not reached its potential yet. Betterman et al. pointed out its main cause as uncertainty in regulatory flexibility and recommended the strategic use of risk assessment tools, beginning with available ones instead of using all aspects of QbD at once, to enhance product development and fulfil regulatory needs7.
Critical review

In 2010, ICH’s Quality Implementation Working Group released Q8/ Q9/Q10 Questions & Answers (R4) to point some details about design space, real-time release testing and control strategy.

Four main elements of QbD are (i) risk assessment approaches which begin with mapping tools such as flow-down map, process map, Ishikawa diagram to evaluate their knowledge space and further risk management tools such as failure modes and effects analysis (FMEA), (ii) PAT tools including in-process monitoring and multivariate systems, (iii) mathematical and statistical tools which can be used in the planning, designing and analysing the experiment: statistical design of experiments (DoE), (iv) continuous improvement tools which are implemented throughout process/product lifecycle to maintain the robust QbD construct. The aim of this review was to discuss the history of pharmaceutical QbD at a glance.

QbD continuum

**Identifying target product profile and quality target product profile**

The target product profile (TPP) is a summary of the drug development programme described in the context of prescribing information goals. TPP is basically expressed in clinical terms such as indications and usage, contraindications, warnings, adverse reactions, overdose, etc.

The quality TPP (QTPP) includes some aspects of the TPP which can be controlled by the formulation/process and applies quality targets to these patient-relevant characteristics such as assay, content uniformity and stability.

**Identifying critical quality attributes, critical process parameters, critical material attributes and their relationship with critical quality attributes**

A critical quality attribute (CQA) has been defined in ICH Q8(R2) guidelines as ‘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’. Product CQAs can be determined based on prior knowledge, identified QTPP and risk assessment, and they should always be considered during the formulation and process development. For example, sterility is considered as an essential CQA for all sterile products.

CPPs and CMAs are process parameters and material attributes whose variability has an impact on a CQA and therefore should be monitored or controlled.

Identification of CQAs is done through risk assessment as per the ICH guideline Q9. Prior knowledge from past non-clinical and/or clinical experiences with a specific product quality attribute, data from similar molecules and literature references can be used as key factors of the risk assessment.

Risk management tools are essential in every step of the quality risk management process. First, by the use of mapping (basic risk management facilitation methods), the knowledge space should be defined. Flow-down map, process map and Ishikawa diagrams are common tools. Such tools as FMEA, failure mode, effects and criticality analysis and hazard operability analysis are generally used for risk assessment during manufacturing, especially for understanding the impact of every operating parameters on overall process performance.

**Process development**

The aim of this stage is to confirm the dependences and to quantify the effects of relationship between CPPs/CMAs and CQAs with DoE studies, statistical and/or mechanistic models and PAT tools.

The most preferred screening DoE studies are factorial and Plackett-Burman designs while Box-Behnken and central composite designs are commonly used as optimisation DoE studies.

**Design space**

Design space is defined in the ICH Q8(R2) guideline as ‘the multidimensional combination and interaction of input variables (e.g. material attributes) and process parameters that have been demonstrated to provide assurance of quality’, and a statement that is ‘working within the design space is not considered as a change’ was emphasised.

There are different ways for establishing a design space including the

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Critical review

First principles approach, empirical approach and scale-up correlations. When multiple variables are considered on the same CQA, a factorial design can be combined with linear and multiple-linear regression analysis to develop design spaces via the empirical approach.

Criticality analysis
With the aim of identifying process parameters and/or material attributes that require tight monitoring and control, final criticality analyses are conducted.

Control strategy
Control strategy is a planned set of controls derived from current product and process understanding that assures process performance and product quality. At this stage, PAT tools are essential to show the assurance and its level of dependence on a given monitoring capability.

Lifecycle management
New findings from industrial manufacturing, outcomes of increased understanding with the use of QbD and new advances in technology can be used to improve product quality continuously. Regulators mostly focus on enhancement of quality while increased production efficiency is seen more important by manufacturers. Figure 2 shows an overview of QbD continuum.

Discussion
The authors have referenced some of their own studies in this review. The protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed.

Industry, academia and regulatory bodies need to work together to make QbD implementation widespread. The QbD pilots of FDA which are Office of New Drug Quality Assessment Office of Generic Drugs and Office of Biopharmaceuticals and also QbD and PAT Sciences Network of the European Federation for Pharmaceutical Sciences are encouraging the progress and provide information that supports the concepts of QbD.

For this goal, during the last decade, several case studies of QbD from development of analytical methods to biopharmaceuticals and clinical research studies have been published.

Bulk powder development
According to a study given by Winters and Neves, the main stages of the preparation of bulk powder were synthesis, excipient addition and spray drying. The spray drying was identified as a crucial stage for all CQAs which were determined to be purity, residual solvent level, particle size distribution and bulk density. Potential CPPs were identified by risk assessment as diameter of nozzle orifice, nozzle pressure, outlet drying gas temperature and temperature at exit of the condenser. Eleven runs were performed via 2^4 half factorial design, with the centre point run in triplicates for screening study. Therefore, knowledge space was defined. Then, a central composite design was run with two centre points with three CPPs (except diameter of nozzle orifice) as variables. Uncertainty analysis was conducted for considering model prediction errors to narrow the design space, and, in this way, confidence levels for the preferable operating range were defined. It revealed that the control of equipment which had a certain distance between normal operating ranges and design space had been already obtained.

Comparison study on capsule development
Betterman et al. published a comparison study with traditional and QbD approaches on two products: Tradium and Qbidium. They were in the same capsule dosage form and had the same manufacturing process, but QbD was implemented only in Qbidium. In this way, contributions of QbD tools to the manufacturer were presented realistically. Tradium studies began with making a general product description and poorly defined manufacturing process. Formulation scientists worked with only one-factor-at-a-time studies, consequently they missed critical interactions such as the interaction between the product temperature and the spray rate in Würster coating. Its reflection came as extended regulatory review time. The results of in-process dissolution tests went out of limits with time, and scientists did not have enough product and process understanding to point the actual cause. On the other hand, for Qbidium, QbD continuum

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was started with initial QTPP identification. A flow-down map and a process map were created to outline whole work and gave the details unit by unit, respectively. After two risk assessments, wet granulation, extrusion and spherisation steps were defined as possible risk sources, and further risk assessment was run with the DoE software. Screw speed was found critical rather than die size within extrusion parameters. Without QbD approach, this information would be difficult to gain. For example, in the absence of knowledge about the die size which was found to be non-significant, it could have been considered as a critical factor if any response related to other unintentional changes was obtained in a one-factor-at-a-time experiment. In the end, after a number of failed batches, Tradium was manufactured at commercial scale like Qbidium. The time spent in the early development of Qbidium seems longer but gained knowledge faster and a more robust process2.  

Formulation development of orally dispersible tablets
Charoo et al. studied on the development of diclofenac orally dispersible tablets through a QbD approach. QTPP was made clear. Active pharmaceutical ingredients, excipient and process attributes were determined based on QTPP, preformulation studies and previous experience. Severity of hazards and probability of occurrence were scored and risk ranking was performed. Determined QQAs such as appearance, hardness, friability, dissolution, content uniformity and disintegration time were further studied with a number of factorial design studies. The control strategy was developed after the estimation of residual risk and an assessment for its acceptability. The disintegrant amount and the compression pressure were found to be CPPs in their effects on the disintegration time and the dissolution of tablets. With various combinations of hardness and disintegrants, desired disintegration time was achievable in the larger area of design space. For the blend homogeneity, a combination of blend time, blender speed and drug particle size was selected as CPPs. With less than 7.6 kN compression force, tablets showed acceptable disintegration time and content uniformity. Adherence to design space provided the flexibility for real-time batch releasing12.  

Experiments on compositions of bilayer tablets
Busignies et al. used statistical analysis with 25 bilayer tablet compositions to determine the relation between experimental factors (the effect of the elasticity of both layer materials and the difference of total elastic recovery) and the response variable (breaking force). For five materials including hypromellose and microcrystalline cellulose, different values of total elastic recovery and breaking force were found. To evaluate the correlation, fit method and analysis of variance (ANOVA) were used, and by them it was shown that the model is statistically significant and there are significant differences between the effects of the factors. With the use of a contour plot, a final statement was created which means that elastic recovery of the first layer and the difference of elasticity between the two layers should be minimised to achieve bilayer tablets having a high cohesion. These findings brought important background knowledge for further bilayer tablet formulations19.  

Development of botanical drug products
Zhang et al. implemented QbD to develop the manufacturing processes of botanical drug products. The ethanol precipitation step was chosen as a unit operation in the manufacturing of the dry root of Salvia miltiorrhiza, and its performance was assessed via CQAs which were determined as the recovery of four active ingredients and the removal of saccharides. The CPPs/CMAs were identified as density of concentrate, ethanol consumption and settling temperature with the use of Ishikawa diagram analysis and FMEA. Their effects on CQAs were investigated through a response surface methodology, a Box–Behnken design with four centre points, and it was revealed that higher density of concentrate leads to higher removal of saccharides and lower recovery of active ingredients. Through the enlarged point of view obtained with QbD, all different levels of interactions will be able to be discussed20.  

Development of sterile products
Since QbD can play an important role on the advanced control of manufacturing, which is necessary to achieve and maintain desired sterility, Riley and Li discussed QbD parameters for sterile products over a patent21 which was about an injectable microsuspension where the particle size distribution was stabilised by phospholipids, aimed to show the points that could be implemented in the QbD approach. In this case, pH and sterility were considered as CQAs and a design space was established covering the impact of the concentration of phospholipid, the concentration of thermoprotectant, the pH of the formulation and the level of heat input13.  

Development of nanoparticles
Yerlikaya et al. evaluated poly(lactide-co-glycolide) (PLGA)-based nanoparticle formulations of paptita. With an Ishikawa diagram, a knowledge space was created which pointed out eight formulation and process variables. Based on prior knowledge, average particle size, zeta potential and encapsulation efficiency were considered as CQAs. A Plackett–Burman design was conducted with...
eight factors in 12 runs. Multilinear regression analysis and ANOVA were performed. Effects of five factors were found to be statistically insignificant. Considering the results of the screening design, a three-factor, three-level Box–Behnken design was applied for the optimisation of formulation and process parameters. Selected variables were PLGA amount in organic phase, surfactant concentration in aqueous phase and the homogenisation rate. Regression analyses were carried out to derive a polynomial model for the estimation of the average particle size and the encapsulation efficiency. By the use of gained information via design space, the lowest level of surfactant concentration, the highest level of homogenisation rate and medium level of PLGA amount were chosen as inputs. Thus, a desirability value of 0.89 was found, which indicated a closeness to the desirable set of response values.

Development of nanosuspensions
Ghosh et al. studied on the optimisation of CPPs of top-down media milling process with naproxen. With a factorial design focusing on three parameters, effects of the size of grinding media and drug content were not found to be as significant as agitation rate which had a great impact on the particle size distribution. After identifying non-critical parameters, they continued with the investigation of different polymers, and hypromellose showed superior results in producing nanoparticles and inhibition of crystal growth during storage.

Development of an in situ implant formulation
Ibrahim et al. implemented QbD into development of an in situ implant formulation of meloxicam. Optimisation through Box–Behnken design was conducted with the PLGA level, N-methyl pyrrolidone level and the PLGA intrinsic viscosity as CPPs/CMAs. Initial burst release of drug, cumulative release and the dissolution efficiency were identified as CQAs. They carried out physicochemical characterisation studies with well-known methods such as scanning electron microscopy. Sprague–Dawley rats were chosen for pharmacokinetic studies of the optimised formulation. The study indicated that while burst release was related to the N-methyl pyrrolidone level, the PLGA level affected the cumulative drug release. Actual responses for the optimised formulation were in close agreement with the values predicted by the model. The desired effect of long-term management of inflammatory conditions was shown through comparison tests with solution formulation.

QbD for biopharmaceutical drugs
Martin-Moe et al. presented a systematic approach including a risk assessment and an experimental design to biopharmaceutical drug product development using a monoclonal antibody as a model drug. In the beginning, a roadmap and a process outline were constructed based on prior knowledge and risk assessment, following the definition of the QTPP. For some product attributes specific to biopharmaceuticals, such as the amount of host cell protein, the targets were determined. Then, a scoring matrix was used for risk ranking and for filtering the quality attributes as a CQA or not. In this regard, aggregation, fragmentation and deamidation were found to be CQAs. With adoption of the same tool, presumptive CPPs for each unit operation were determined to be pH, concentration of surfactant, buffer, tonifier, time and temperature. Effects of unit operations on CQAs were also demonstrated with some assays used for detection. A five-factor, two-level factorial design was used to examine the relationship between CPPs and CQAs and to define the multivariate acceptable ranges. For process validation, small-scale models or at-scale surrogate models for each unit operation were conducted. Proven acceptable ranges, CMAs and design space were also established. With the achievement of a well-defined QbD programme to clarify ranges and specifications of this biopharmaceutical drug product, operating of the system can become more effortlessly for the other monoclonal antibodies.

QbD approach to fluid bed granulation
Laurenço et al. aimed to increase the understanding of the fluid bed granulation process. Granulation of an API with a filler and an aqueous binder, dispersion was carried out in a pilot scale fluid bed dryer and using larger equipment for scale-up experiments. As PAT tools, an in-line moisture analyser and a particle size analyser were used. These analyses were supported with off-line analysers. FMEA was conducted to assess the potential risk factors. The mixing phase was found to be not critical compared with spraying and drying phases. Effects of all CPPs on the CQAs of the granules such as particle size distribution, bulk and tapped densities, flowability and angle of repose were investigated. For screening purposes, a two-level fractional factorial design with 19 runs was applied, considering the impact of the inlet air temperature, the air flow rate in both spraying and drying phases and the binder spray rate in the spraying phase. Since the drying phase was found to be less effective, an optimisation study, just for parameters in the spraying phase, was conducted.
for a better understanding of these excipients and to predict the relationship between CMAs and CQAs. Therefore, orthogonal projections to latent structures were used and the constructed models were validated. It was demonstrated that the tensile strength reduction is not critical for the brittle materials when roller compacted contrary to what is known for plastics. With the interpolation of more fillers, this study can be enhanced to be an in silico method for new compounds without any additional experiments.

**QbD approach to tablet coating**

Dubey et al. operated a QbD case study on the subject of tablet coating uniformity utilising QbD tools to quantify the magnitude of coating thickness variability within a tablet, within a batch and between different batches. Inter-tablet variability was found as the most significant component by a laser-induced breakdown spectroscopy-based analytical method and a statistical analysis. Slow axial mixing in the coating pan which was considered as the root cause of this type of variability was examined with a number of experiments. Pan rotation speed, per cent weight gain and coating temperature were selected as independent variables. A response surface modelling and kriging method were used for optimisation and prediction of design space. Mixing was found as a contributing factor and the effects of spray rate, pan rotation speed and spray temperature were characterised. The results were quantified in terms of the relative standard deviation of tablet-averaged spectroscopy score. This successful study resulted in significantly reduced variance and a robust process for different dosage levels.

**Other studies**

The QbD approach can be very useful to investigate the reasons of some failures. For example, Rahman et al. studied the effect of the ternary system in nimodipine formulations, which were recalled because of the problems related with drug crystallisation.

Barbaroux et al. performed a QbD approach to develop state-of-the-art single-use bioreactors. With regard to QbD, broad expertise and enhanced know-how including the cell culture application, polymer chemistry, regulatory requirements and a deep understanding of the biopharmaceutical industry became even more important.

Awotwe-Otoo et al. showed that QbD approach could be effective to optimise a robust high-performance liquid chromatography (HPLC) method for protein analysis with the least number of experimental runs. A Plackett–Burman design, a Pareto ranking analysis and a Box–Behnken design with response surface methodology were used. After identification of the significant factors such as mobile phase pH, column temperature and injection volume, they investigated the main, the interaction and the quadratic effects of these factors on peak resolution and on the tailing factor. Therefore, an HPLC method for the separation of hydrolysed proline sulphate peptides was successfully optimised and validated.

Zhang et al. aimed to implement QbD tools in physiologically based absorption models. To that end, a model was used to help identify optimal in vitro dissolution conditions for extended-release formulations. Identification of critical formulations variables was illustrated with the use of a parameter sensitivity analysis. Virtual trial simulations allowed the incorporation of intersubject variability in the model. This study indicated that QbD tools can be very useful in every step of drug development.

Huang et al. utilised QbD tools such as experimental design, response surface modelling and multi-way principal component for root-cause investigation of dissolution
shift upon stability and for the estimation of optimal process conditions. It was demonstrated that optimisation of lubrication time and blander speed during lubrication can provide faster dissolution with minimal shift upon stability.

Conclusion

The QbD approach leads to enhanced understanding, well-defined system and regulatory flexibility. Well adoption of QbD tools is the key to achieve long-term benefits. Not to be disoriented among all aspects of QbD, appropriate risk assessment tools such as flow-down maps and Ishikawa diagrams can be considered in the beginning. It will be instructive to keep the processes in perspective. Tools of DoE and PAT should be determined based on the specific intentions and to make their outcome assessment capably, well-trained staff are necessary as well as for establishing a design space which requires mathematical and statistical knowledge. As shown with mentioned case studies, implementation area of QbD is extremely wide. QbD can provide extended knowledge about all phases in any drug’s lifecycle. In product development studies, combination of several material attributes and unit operation parameters are evaluated. But, it is also possible to focus on only one unit operation such as fluid bed granulation, roll compaction and tablet coating. With the contribution of different bodies of the pharmaceutical area, all of the case studies exemplify to encourage the implementation of QbD. As long as pharmaceuticals get more complex in the meaning of advanced manufacturing techniques and the new areas such as personalised medicine, the importance of a well-constructed quality system will gradually increase.

Abbreviations list

ANOVA, analysis of variance; cGMPs, current good manufacturing practices; CMA, critical material attribute; CPP, critical process parameter; CQA, critical quality attribute; DoE, design of experiments; FDA, Food and Drug Administration; FMEA, failure modes and effects analysis; HPLC, high-performance liquid chromatography; ICH, International Conference on Harmonisation; PAT, Process Analytical Technology; PLGA, poly(lactide-co-glycolide); QbD, quality by design; QTPP, quality target product profile; TPP, target product profile.

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