

New Quality Concepts in Pharmaceuticals

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ÖZET

Farmasötiklerde yeni kalite kavramları

Büyük hızla yeniliklere adapte olmaya çalışan ilaç sanayii, son yıllarda, üretim bilgilerinde, kalite yönetim sistemlerinde ve risk yönetiminde önemli ilerlemeler yaşamış ve üretim kalitesinin sağlanmasına yardımcı olmak için kullanılabilecek modern üretim araçları geliştirmiştir. Bu yeni araçlar üreticilerin problemleri saptamasına, analiz etmesine, düzeltmesine, önlemesine ve üretim süreçlerini sürekli olarak iyileştirmesine yardım etmektedir. Bu gelişmeler üzerine, 2002 yılında Amerikan Gıda ve İlaç Dairesi (FDA), ilaç üretimini düzenleyen kuralları ve ürün kalitesini daha da geliştirmek ve modernize etmek amacı ile Güncel İyi Üretim Uygulamalarındaki (cGMP) yenilikleri ilaç endüstrisine duyurmuştur. ABD, Japonya ve Avrupa'da ilaç endüstrisinin yetkilileri ve uzmanlardan oluşan, ilaç ürünleri için teknik gereksinimlerin bu üç bölgede uyumlaştırılması amacıyla kurulmuş bir forum olan Uluslararası Harmonizasyon Kurumu (ICH), endüstriye Tasarımla Kalite (QbD) olarak adlandırılan yeni bir yaklaşım getirmek için güncel kılavuzları (ICH Q8, Q9, Q10 ve Q11) yayınlamıştır. Kaliteyi test etmek yerine tasarımla sağlayan bu yeni yaklaşımın bir sonucu olarak, üründe kalite artışı, üretim maliyetinde azalma ve ürünün piyasaya daha kısa sürede sunulması sağlanmaktadır. Ayrıca, hastanın güvenliği ve daha kaliteli ilaca daha kısa sürede ulaşması üzerinde durulmaktadır.

Anahtar sözcükler: Üretim Kalitesi, ICH, Tasarımla kalite

ABSTRACT

New quality concepts in pharmaceuticals

During the recent years, the pharmaceutical industry, trying to adapt itself to innovations by leaps and bounds, has experienced major developments in production information, quality management systems and risk management, and has developed modern production tools that can assist in ensuring the production quality. These new tools help the manufacturers identify, analyze, correct and prevent problems, and constantly enhance the production processes. Therefore, in 2002, the Food and Drug Administration (FDA) introduced to the drug pharmaceutical industry the amendments in the current Good Manufacturing Practices (cGMP) to improve and modernize the rules that regulate the pharmaceutical product manufacturing and the pharmaceutical product quality. International Conference on Harmonization (ICH) is a forum that gathers the authorities and experts of the pharmaceutical industry in the USA, Japan and Europe to harmonize the technical requirements for pharmaceutical products in these three regions, published current guidelines (ICH Q8, Q9, Q10 and Q11) to bring a new approach which called Quality by Design (QbD) to the industry. As a result of using the new approach of providing quality by design rather than testing it, quality increase, cost reduction and faster market access have been achieved in manufactured products. Moreover, patient safety is emphasized and quicker access to pharmaceutical products by the patient is ensured with a higher quality products.

Key words: Production Quality, ICH, Quality by Design

INTRODUCTION

Pharmaceutical authorization process has high needs and requirements that increase the labor and costs. Risks also increase in parallel with complex practices in the pharmaceuticals industry. Although it is difficult to

eliminate complexities leading to increased risks, there is need to correctly manage risks and likewise arrange decision making processes (1).

The length of the approval process has led to concerns in the pharmaceutical industry for many decades. Today, it is known that this process, which involves large paperwork for

evaluation and approval of new product submissions, is slow, cumbersome and causes excessive delays. In addition, the attempts to introduce new pharmaceutical products to the market are seriously interrupted due to “stalemates” in pharmaceutical product development and the requirement to start over for a development cycle of any changes, even after the pharmaceutical product and its process is licensed (2).

Pharmaceutical industry has been trying hard to adapt itself to innovations rapidly in the last years and it has witnessed major improvements in terms of product information, quality management systems and risk management. As a result, modern production tools are developed to support the manufacturing quality. These new tools assist manufacturer companies in identifying, analyzing and preventing problems, as well as improving the manufacturing processes. Accordingly, Food and Drug Administration (FDA) introduced the Good Manufacturing Practices (GMP) to the pharmaceutical industry in 2002. These GMP rules aim to improve and modernize the regulations within the pharmaceutical product manufacturing as well as the product's quality. cGMP offers a wide scale of set of regulation tools to facilitate achieving the desired conditions. As a result of the cGMP initiative, innovations have been brought into the drug pharmaceutical industry; however, they are not yet mandatory for implementation (3).

ICH is a forum that gathers the authorities and experts of the pharmaceutical industry in the USA, Japan and Europe to harmonize the technical requirements for pharmaceutical products in these three regions, and one of its tasks is to publish current guidelines (4). In this framework, the guideline Q8 was published in 2005, which introduced the concept of Quality by Design (QbD) into the pharmaceutical industry (5). Later on, as one of the important steps to defined QbD requires a distinction between the critical and non-critical product qualities and process parameters, it was decided that there was a need to conduct and manage risk assessments, and the ICH guideline Q9 was thus published (6). Finally, the last document of the triple structure, the guideline Q10 was published to regulate the quality management system of pharmaceutical product manufacturers, which establishes the expectations from the Pharmaceutical Quality System, and deals with the ways of their implementation in

achieving compliance with quality standards in design, quality management, and risk assessment during the life-cycle of the product (7). The studies on guidelines following the above continued with the guideline Q11 on manufacture of pharmaceutical raw materials (8).

1. Science and Risk Based Approach

As defined in Q8 guideline of International Conference on Harmonization (ICH), QbD is a systematic product development approach that begins with pre-defined objectives and emphasized understanding of the product and process based on firm science and quality risk management (5). Two basic components of QbD are quality risk management and knowledge management.

1.1. Risk Based Approach

Adoption of risk based orientation by the FDA is the most important aspect of the twenty first century cGMP. FDA has carried out a pilot study in 2005 including risk rating model. The model is based on a hierarchical risk assessment and risk filtering method and a Site Risk Potential (SRP) calculates the site risk as a function of weighted potentials for each of the three high level components of site risk, as product, facility and process. The risk potential for these three high level components is a function of the relevant selected risk factors. A sub-category set has been defined for each high level component and each sub-category comprises of different risk factors (9).

Renewals of risk rating models are carried out through establishing correlation between control activities of projected risk potentials and collected data; and by arranging risk factor weights in order to maximize accuracy of SRP prediction (9).

1.2. Science Based Policies

In the manufacture of a pharmaceutical product, especially taking into consideration the financial and ethical pressures on process development teams carrying out works to release a new pharmaceutical product to the market, there is a problem about the idea of considering the first confirm configuration as the most suitable one. This situation has resulted in the authority initiating the

process of developing science based policies and standards in order to support innovation, thus new guidelines have been generated. Each guideline gives incentive for willing adoption of new technologies in pharmaceutical manufacturing, by defining modern, science-based authorization processes that allow manufacturers to carry out easier authorization processes and improvement works (9).

1.2.1. Comparability Protocols (CP)

The difference between the classical authorization model and the cGMP initiative is to ensure that manufacturers that seek to increase quality and efficiency spend considerably less amount of resources to maintain comparability and carry out changes much faster. These works indicate that sufficient understanding of the process and the changes to be made and the improvements shall cause very low risk for consumers. Implementation of process changes has been explained in detail in the FDA CPs and Chemistry, Manufacture and Controls (CMC) information (10).

2. QbD Applications

Quality of a pharmaceutical product is dependent on understanding molecule reliability, mechanism of action and its biology. Understanding, control and pharmaceutical quality is ensured for formulation and manufacturing variables, when QbD is used. Manufacturing process is developed according to development and fulfilling of requested features of the molecule; in case product quality is "designed" rather than "tested" (11). In the QbD approach, it is possible to use data obtained from development works carried out to create a design space for achieving continuous development and existing information. This way, it is possible to provide changes in the industry through change control method, without confirmation from the authority. Also the most up-to-date pharmaceutical and engineering information is used during the life-cycle of the product. In addition to this, QbD works inside the design space obtained by considering critical formulation and process parameters and therefore no need remains for product quality verification through final quality test. Processes are adopted with the help of Design of Experiments (DoE) and

PAT instruments with quality management, in order to create a product that has the same quality continuously, and the products are very well understood (12-14).

2.1. QbD Steps

Using Previous Information

Management of product and process information is an indispensable component of design and quality and should be continued throughout the whole or entire full life-cycle of the product. In QbD, it is necessary to ensure flow of information from development to manufacture and flow back from manufacture to development and transparency of information is a must (14).

Pre-existing information consists of understanding of what is successful and what is not, a possible problem, risks or defining of which issues are to be taken into consideration. Usage of pre-existing information constitutes the basis in phases such as risk assessments and experiment designs and their usage in QbD is extremely necessary (14).

2.1.1. Design Targets

The first step in QbD is determining design objectives for the product.

2.1.1.1. Target Product Profile (TPP)

Target Product Profile (TPP) described the general objective of the pharmaceutical product development program and provides information about the development works. Generally TPP includes certain concepts that are required on the label of the pharmaceutical product (15). Among them are route of administration, form and dosage, maximum and minimum doses, presentation of pharmaceutical product and target patient population (16). In pharmaceutical development, ICH Q8 requires "determining of features critical for quality of the ready-made pharmaceutical product, with regard to intended use and route of administration" and assessment of intended use of the product and route of administration is carried out through the TPP. TPP is a patient and labeling based concept and can be considered as the "user interface" of the ready-made pharmaceutical product. Therefore, TPP is expected to be the same for a generic and the reference product (5).

2.1.1.2. Quality of Target Product Profile (QTPP)

Quality profile of target product, or in other words quality of target product profile (QTPP) is quantitative support for clinical safety and efficacy that can be used for designing and optimizing a formulation or manufacturing process. QTPP constitutes the basis of product development and begins by "design in the mind". QTPP is a sub-branch of the TPP published by the FDA and is focused on the chemistry, production and control phases of development (16). QTPP only includes product performance related to patient.

2.1.1.2. Critical Quality Attributes (CQA)

The concept of criticality can be used to explain any feature, importance or characteristics of an active substance, component, raw material, finished product or device; or any process characteristics, parameters, conditions or factors in finished product production (5).

International Society for Pharmaceutical Engineering (ISPE) defines Product Quality Lifecycle Implementation (PQLI) as critical quality attributes (CQAs) as physical, chemical, biological and microbiological features/ characteristics that should be directly or indirectly controlled in order to ensure product quality. This CQA definitions indicate that targeted safety, efficacy, stability and performance is not CQA. Security and efficacy is under the scope of TPP (14).

2.1.1.3. Critical Process Parameters (CPPs)

A parameter expresses a characteristic of a system or process that is measurable or countable. Parameters are usually considered as features related to manufacture, such as temperature, mix speed, or as characteristics of equipment or process; on the other hand, features are considered as characteristics of materials (such as melting point, viscosity, sterility). However, it should be kept in mind that there are no absolute borders between features and parameters (17).

There are many material features and process parameters which are necessary to achieve required product quality and should be monitored and controlled; however, all parameters may not be critical. Separating

characteristics or parameters as critical or non-critical is an important result of the development process.

The most accurate method for determining critical and non-critical parameters is scientific research on controlled variation of parameters. The focal spot of the process development report is the information obtained from pilot and laboratory scale works that generate this information and such works do not have to be carried out under the scope of GMP applications (17).

CPPs in the product life-cycle may change and new critical process parameters may emerge, as new information is obtained and understanding about process is developed; or the acceptable ranges of these parameters may change depending on process understanding and product improvement. It should be kept in mind that all these changes can affect the process and design space (14).

2.1.4. Design Space

Design space is defined as "multi-dimensional combinations and interactions of input material variables (i.e. material features) and process parameters with proven assured quality". Design space is specific to a single unit operation, multiple unit operation or a single manufacturing process and defines operational process parameters that are known to affect product quality. Design spaces can be considered as the link between CQAs and CPPs (18).

Development process of design space starts with the idea of the product to be produced and continues throughout the life-cycle of the product. Design space, is dependent on the concept of criticality, due to results of risk assessment that determines which critical features and critical process parameters are to be included in the design space (19).

Design spaces can be generated with data obtained from experiments. However its limits can also be determined by risk management. These limits can be based on critical material features and critical process parameters; as these features and parameters are independent of scale and equipment, it becomes easier to make change in scale and equipment (20).

Boundaries of the design space should be very well defined. Information should be provided on which parameters and ranges are included in the design space. An explanation should be made when ranges investigated at

laboratory scale do not coincide with the design space. Comprehensive information about design of experiments and statistical methods should be included in the application (2, 20).

As stated previously, design space describes the multi-variable functional relations between CQA and the CPPs that affect and includes their relation to unit operations. These relations can be reached through joint application of risk assessment and DoE and modeling, as well as using the literature and previous information (21).

2.1.4.1. Design Space and Modeling

The most important supporter in developing design space is in many cases, generating process models. A model is a representation of the underlying complex physical and chemical events. Experiment efficiency can be increased and it can be guided, also a deep process understanding can be generated. Experiment and modeling are inseparable applications; experiments have a vital role in determining factors to be worked on and modeled. Modeling stands out more in the new phases, but experimental and observational data are needed in order to prove effectiveness of the model (22).

In formation of design space, model based information display and previous process information of the product are more effective than the effect of information from other products and processes. Even if quality level expected from a certain combination of formulation and process parameters taken from another product shall not be carried over to a new product or process, similarities of functional relations shall help. Model based design space allows for direct addition of information and this is effective for process development (16, 21).

2.1.4.2. Risk Assessment Practices

Starting point for developing design space is a risk assessment application, where risks are assessed to reach QTPP, which is considered as an expression of CQA acceptance criteria. Risk assessment concludes with; defining of fields with risks accepted as related to process and defining of fields that require detailed work for reducing or controlling risks or developing more understanding in case of risk (20). Risk assessment should be repeated at

different times during product development phase and turn into a risk management application throughout the commercial life-cycle of the product.

2.1.4.3. Design of Experiments (DoE)

Parameters to be included or excluded to multiple variation analysis and/or model development for generating design space; should be assessed and selected carefully; within significant differences between process requirements for large and small molecules; as well as differences between active substance and finished product production phases. Number of parameters for multi-factorial analysis should be reduced when process parameters are defined. Effort to generate a design space that includes all parameters that could affect the quality of finished product can be long and exhausting. For this reason, risk analysis instruments can be used to point at parameters with decreased risk of really affecting a CQA in a finished product (20, 23).

Other than risk assessments, alternative or different other instruments can also be used for deciding on the most suitable scope of the experimental program. For example, in case of a fully developed first principle model; model predictions can be developed in determining potentials of multi-factorial interactions in the relevant range, for all modeled parameters. Optimized parameters can be referred, in order to generate a design space where results are clearly seen within relevant ranges as multi-factorial form, for use model predictions and designed experiments. In order to reduce the experiment load necessary for model verification or experiment design, generally it is also possible to divide parameter sets into logical groups. Small groupings can be made in product development, by working on parameters related to single unit operations (23).

2.1.4.4. Problems Related to Design Space and Scale

Development of design space is usually carried out at laboratory scale, due to scarcity of used materials, easy use of equipment and repeatability of experiments. Understanding risks related to scale-up regarding features and parameters in the design space, indicates the need for works for the purpose of suitability of the design space on a commercial scale.

2.1.4.5. Formal Display and Presentation of Design Space

Presentation of design space is very important in the pharmaceutical drug industry, where reliability and transparency are indispensable principles throughout the life-cycle of a product and which is surrounded by regulations. Presentation of the design space should start with a brief guideline describing the process used during development, in order to evaluate criticality, define design space and determine acceptable control strategies (19).

Risk assessment works should be explained. And this includes defining of functional relations between CQAs and their process parameters, and other quality characteristics that can affect them. In cases where information was received from previous information or literature sources, sufficient connections should be provided for evaluators to see the link between previous information and the current application. The relation between risk assessments and CPPs and the models and experiment plans used to define their acceptable operation areas, should also be examined (19).

2.1.5. Control Strategy

There should be a control strategy in all products, simple or complex, whether developed in minimal approach or advanced approach (as QbD). In products developed with QbD approach, in-line controls are mostly used in the control strategy (23).

The control strategy in ICH Q10 is defined as a planned controller set deducted from current and process information that assures process performance and product quality (7).

The control strategy should be generated; however the control strategy can also be established by using the quality risk management principles specified in ICH Q9. Results of risk assessment determine critical quality features and critical process parameters, that should be included in the design space and which should later be included in the control strategy (21).

If necessary, the pharmaceutical quality system should be updated to support the QbD approach in the control strategy. Pharmaceutical quality system should provide the technical and management auditing in order to obtain the

assessment and approval necessary for changes in product information, documents, operation procedures and systems (23).

2.1.5.1 Control Strategy and Real Time Release

PAT instruments can be utilized to achieve a comprehensive process understanding and process control. In-line and at-line PAT usage can be useful in certain cases for reducing laboratory tests by allowing for Real Time Release (RTR). PAT, which is a part of the control strategy under QbD, is defined as a system for "design, analysis and control of manufacture, by timely measurement of critical quality and performance features of raw and process materials and processes, for the purpose of achieving finished product quality target" (16).

2.1.6. Process Monitorization

Process performance and product quality monitorization systems, which include finished product manufacture process parameters, and material and product features, have many benefits as opportunity to decrease process variations, prediction and prevention of defective serial production, increase in process understanding and waste reduction. During monitorization, through inter-series and intra-series statistical and trend monitoring, conformity is achieved with Lean Manufacturing activities (23).

3. Concerns and Questions (Problems) about QbD

Cost: The pharmaceutical industry still has concerns about its effect on cost and the position of the product on the market. There is the perception that the benefits of change would not worth it, general unwillingness of the industry to put forth changes to authorization institutions and reluctance to make changes in processes (24, 25).

Harmonization: The new paradigm should be fully understood and implemented. Lack of harmonization across all countries is considered to make a negative effect on the future in terms of application of ICH Q8, Q9, Q10 and Q11 guidelines. Different variation application procedures shall be on the agenda if variations are made on products (24, 25).

Expertise/New techniques: Regulatory authorities, auditors and industry employees should receive training about QbD, which uses more comprehensive approaches and different techniques, DoE and statistical instruments. Expertise is necessary for examination of QbD marketing authorization application files and other post-approval applications and evaluation of presented data (24, 25).

Dialogue of Industry and Authority: The dialogue and continuous communication among the industry, evaluators and auditors should be maintained. Applicants shall determine the approach to be implemented according to product and process complexity. Justification should be based on scientific information in applications (for example detailed description of the implemented control strategy). As questions regarding specific information to be requested by evaluators in terms of description of applied approaches and a need for mutual information exchange may arise, it is important for the applicants to establish dialogue and maintain continuous contact with evaluators (24, 25).

GMP: It should be kept in mind that QbD application does not change authorization requirements, only results in a more flexible approach in terms of both applicants and evaluators. GMP requirements must be applied in all cases.

Misunderstandings and Mistakes: It has been observed that there have been common misunderstandings in the QbD license application files. Some of these are related to definitions. It is considered that QbD applications shall be examined in more detail and that it shall take more time during approval process, due to higher number of questions and audits prior to approval. It has been observed that the concept of design space is regarded to be same as DoE, and that release is carried out based on design space and specifications are not found necessary. One of the common mistakes made is considering that a parameter that has been controlled would no longer be critical (24, 25).

4. Solutions and Benefits Put Forth by QbD

Primarily QbD applications put forward a win-win-win policy. From the perspective of manufacturers; better understanding of product/process, development of more

effective processes and less regulatory requirements are possible. Achieving regulatory flexibility without reducing quality is important for regulators also.

In the current situation of the industry, it is observed that investment on manufacturing operations is much less compared to Research and Development. It is estimated that savings from manufacturing efficacy improvements shall be 90 billion dollars throughout the world; which corresponds to cost of developing 80-90 new drugs each year (26). As new technologies (QbD, PAT) are applied, this situation of "focusing" is expected to become more balanced. Rather than a recommendation, this has become a necessity, considering the public health mission of pharmaceuticals (efficacy, reliability and quality).

In using QbD, methods with PAT applications usually reduce exposing of operators to chemicals and/or potential hazardous products in non-procedural methods and sustainability of environment friendly applications are supported. With use of on-line and in-line techniques, tests necessary for serial release are reduced; therefore, removal of waste solvers decreases the costs necessary for recycling and reduces analysis times. Continuous process improvement becomes possible with application of the control strategy that uses developed approach and formation of defective series can be reduced (23).

On the date an application is made, the design space shall reflect the existing process information at that date. Additional information at the commercialization phase of the product may bring about post-regulatory changes. However an application/ approval process is not required for changes to be made in the design space; a licensing authorization state that opens space for selected parameters, but does not allow flexibility to other parameters, is achieved. Going outside the design space is regarded as a change and requires initiation of a normal post-regulatory change (variation) process (16, 21).

Design space provides very high degree of reliability for pharmaceuticals quality and performance, especially when linked to control strategy and criticality evaluation; and it can change authorization approaches with the data it provides. For the industry, it allows for more effective dialogue between the industry and authority, by presenting a very advanced and planned approach, strictly bound to product development with risk based and scientific approach (19).

In addition to these, it allows for understanding critical and non-critical parameters in developing design space, and provides opportunity for focusing on important parameters in product quality in validation works. As the control range where product and process are not affected, is better understood than an empirically generated range, a wider validation acceptance criteria is achieved (22).

CONCLUSION

Product quality cannot be tested at the end of manufacturing process using QbD approach, but quality is designed at product design phase and quality is embedded in the product. Rather than controlling quality, quality assurance is ensured, which is more superior (5).

Manufacturing implementations with continuously constant processes have ended with generation of a full understanding regarding the process; and process is made dynamic through approaches based fully on scientific data and implementations based on previous information and experience, along with determining and managing critical

points through risk management implementations, by determining critical points regarding product and process (17).

Development and innovation are hindered as a result of processes and systems that are not changed. However, with the design space brought by QbD, flexibilities such as real time release have become a part of the process. As a result of these changes, operability of the processes has been proven and reliance on the system has increased.

Testing of quality in process begins as the process is halted and testing is removed. Controls have been carried out based on critical features in the process and changes made in relation to these have been managed and the process has been continuously advanced. As continuous process improvement has become possible, an approach implementation has come where process performance intended for process validation is continuously monitored, evaluated and adjusted (17).

Most importantly, other than these, this new approach has allowed for acting and decision making with scientific and risk based information.

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