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Review article

The Place of Drug Product Critical Quality Parameters in Quality by Design (QBD)

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Along with the fast developments in the drug production and control technologies, it has been easier to comment on the drug and its production, as well as observing/seeing the defects. These developments have brought within new arrangements in the regulations. Recently added ICH Q8, Q9, Q10 and Q11 guidelines have aimed to make the drug industry to develop rather an information based understanding towards the drug. Within this frame, especially during the drug formulation and active substance development studies, all factors that may affect the quality of the drug should be examined with scientific/statistical methods. For drug development that is compliant with the regulations, proper understanding and interpretation of new concepts explained in the guidelines are initially necessary. Some of these new concepts are Quality by Design (QbD), Critical Quality Attributes (CQA) and Critical Process Parameters (CPP). Each dosage form has its specific Design Space, Critical Quality Attributes and Critical Process Parameters. Correct determination of these parameters and values during the formulation development studies decreases the possible problems related to the drug throughout the drug's life cycle and help them to be eliminated entirely. Therefore, it contributes to provide the quality that is expected from the drug.

Key words: Critical quality parameters, Critical quality attributes, Pharmaceutical development, Risk assessment, Quality by design, Quality target product profile.

Tasarımla Kalitede Bitmiş Ürün Kritik Kalite Parametrelerinin Yeri

İlaç üretimi ve kontrolüne yönelik teknolojilerde meydana gelen hızlı değişimle birlikte ilaca ve üretimine dair yorum yapmak ve hataları gözlemlemek/görmek daha kolay hale gelmiştir. Bu ilerlemeler, beraberinde regülasyonlarda yeni düzenlemeleri de getirmiştir. Yeni eklenen rehberler ICH Q8, Q9, Q10 ve Q11ilaç endüstrisinin ilaca yönelik, daha çok bilgiye dayalı bir anlayış geliştirmesini hedeflemiştir. Bu çerçevede özellikle ilaç formülasyonu ve etkin madde geliştirme çalışmaları sırasında, ilacın kalitesini etkileyecek tüm faktörlerin bilimsel/istatistiki yöntemlerle ele alınması gerekmektedir. Regülasyonlara uygun ilaç geliştirme için öncelikle rehberlerde açıklanan yeni kavramları doğru anlamak ve yorumlamak gerekir. Bu yeni kavramlardan bazıları Tasarımla kalite (QbD), Kritik kalite vasıfları (CQA) ve Kritik proses parametreleridir (CPP). Her dozaj formunun kendine özgü Tasarım alanı, Kritik kalite vasıfları ve Kritik proses parametreleri vardır. Formülasyon geliştirme çalışmalarında bu parametreleri ve değerlerini doğru tespit etmek, ilaca ait yaşam döngüsü boyunca ilaca yönelik karşılaşılabilecek problemleri azaltır veya tamamen ortadan kaldırılmasını sağlar. Böylece ilaçtan beklenen kalitenin sağlanmasına katkıda bulunur.

Anahtar kelimeler: Kritik kalite parametreleri, Kritik kalite vasıfları, Farmasötik gelişim, Risk değerlendirme, Tasarımla kalite, Kalite hedef ürün profil

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INTRODUCTION

The term “Quality” comes from the Latin word “Qualitas”, entered French as “qualité” and passed from French to Turkish as “kalite”. The concept of "drug product quality" has been included in the terminology of the pharmaceutical industry and local health authorities for decades. In a literature from 2004, Janet Woodcock defined the quality drug product as a product free of contamination and reproducibly delivering the therapeutic benefit promised on the label to the consumer. In the history of drug, the issues experienced as a result of using low quality and poor strength drug products, such as not being able to obtain any therapeutic effect, diseases' becoming more severe, resistance development against medicines and death cases have forced governments to establish strong and effective nation-wide licensing authorities. By effective licensing in drugs, the use of scientific information and technical skills within a regulatory framework is required. All drugs have to be proven to be of good quality, effective and reliable. Only manufacturing premises' audits and laboratory quality control analyses undoubtly cannot guarantee product quality and reliability. Afterwards, regulations concerning every step of drug production process entered into force. First of them is Good Manufacturing Process (GMP) that was entered into force in Section 501(B) in USA in 1938. Currently, there are over a hundred countries applying the GMP. In these guidelines, general rules for the manufacture of appropriate drugs are described. Through a manufacturing process non-compliant with GMP, the clinical performance of the drug cannot be guaranteed. In order to ensure the harmonization of regulations of drug licensing process, ICH (International Conference on Harmonization), which is a body comprised of the administrative authorities from EU, USA and Japan, published guidelines containing technical requirements for efficacy, quality and reliability (1).

Regarding the pharmaceutical industry, releasing new products into the market becomes more difficult every passing day. R&D investments have decreased in time and this decline accelerates every day. However, the length of life of a drug company is proportional to the R&D studies it performs. In drug development studies, it is demonstrated that there are two factors mostly affecting the success and productivity as a whole (2):

- Possessing the most possible scientific understanding about the drug,
- Being able to eliminate potentially unsuccessful candidate products early in the clinical trials.

In most formulation development studies, due to the failure in achieving desired shelf lives, the need to make changes for the purpose of process modification arises during scale-up. Besides, the product quality is determined by the final product analyses. Somehow, the product quality cannot be established and the quality control is ensured only by the tests conducted on the finished product. As a result of these improvements, new technologies have been invented to develop more innovative, secure and effective drugs and developments in this field are still continuing.

Besides, since it is too difficult to understand the relationship between the product attributes and product quality, U.S. Food and Drug Administration (FDA) guarantees quality under a narrow scope of specifications. With this approach, the importance of specifications increased. However, this increase is not because of their being related to the product quality, but rather because the differences in each of the series with potential therapeutic results could be determined.

FDA implies that, Quality by Design (QbD) (3) has started as a result of understanding that the product quality would not increase further with more tests in the 21st Century’s drug quality concerns. QbD has already been used widely in automotive, semi-conductor and petrochemical industries for a while. Some aspects of the QbD approach have been used for years. For instance, the history of statistically designed tests (DoE-Design of Experience) and factorial design applications dates back to 1920s. A widely used risk assessment tool, FMEA (Failure Modes and

Effects Analysis) was developed by the US Army to assess equipment and system failures and has been applied for years. The concept of building quality into product was documented previously and "quality planning" is a common theme in many areas. The concepts of quality plan, quality control and quality improvement are defined within the concept of quality planning. Quality planning is defined as the process of determining the customer needs and designing a product or process that meets those needs. Although Quality by Design is a familiar concept in other sectors, this is quite new for the drug industry. Quality by design (QbD) has been introduced to the pharmaceutical industry in 2005 (4). This implies us that, even though drugs are produced for the future, the production technologies have fallen behind. However, initiation of the current Good Manufacturing Practices (cGMP) in 2002 and publication of Process Analytical Technology Guideline (PAT) by FDA in 2004 have triggered the modernization progress of the pharmaceutical industry (5). Even though this guideline is focused more on PAT, many principles of QbD were addressed. This was followed by new reports such as the report of the European Medicines Agency (EMA) PAT Team focusing on the possibility that the implementation of PAT might result in real time release and how it would play a leading role in QbD (6).

Health authority encourages and inspects drug manufacturers regarding quality drug manufacturing. Recent developments in this regard have been the enforcement of International Conference on Harmonization's (ICH) Q8, Q9 and Q10 intended to ease the work of both drug manufacturers and health authorities (7-9). ICH developed a vision for a system in drug quality in July 2003. With this vision, ensuring an increase in quality assurance and drug availability for patients and making resource assessment and prioritization easier for licensing agents were aimed. Concepts of "design space" and "quality by design" have been adobted in the pharmaceutical industry together with ICH Q8 Pharmaceutical Development Guideline which is focused on CTD Module 3.2.P.2. content published in 2005 for the first time. One of the important steps in defining QbD is to make the distinction that which product attributes and process parameters are critical or not and risk assessments have been considered for this purpose. Q9 Quality Risk Management Guideline to be used for carrying out risk assessments and examining the potential approaches and tools that can be used to manage the identified risks was published in 2005. Q10 Pharmaceutical Quality System Guideline was published in 2008 and is the final guideline of the triplet. With Q10 guideline published for drug manufacturers to organize their quality management systems, it is stated that, quality could be integrated into the entire life cycle of the product together with Q8 and Q9 guidelines. The draft guideline for Q11 focused on active ingredients was published in May 2012 (10).

As it is already known, development of effective and safe new treatments is a long, difficult and expensive process. Use of the new approach (QbD), which encourages the integration (design) of quality into the product instead of testing the quality, has increased the quality of products and it has become possible to decrease costs and also shorten the times needed to release the drugs into the market (11). Moreover, the patient safety has been featured with a better QUALITY drug and it has become possible to access the drugs within a much shorter time.

As defined in ICH Q8, QbD is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management (7).

The quality of a pharmaceutical product depends on understanding its safety, mechanism of action and biology. When QbD is employed, pharmaceutical quality is achieved by understanding and controlling the formulations and production variables. When "designing" the product quality rather than "testing" it is of concern, the manufacturing process should be developed depending on the ability in the development and maintenance of the desired quality features of the molecule. In QbD approach, it is possible to use the information obtained from the development studies to create a design space in which the continuous improvement is achieved, as well

as the information already available. This way, it is possible to ensure changes in the industry by the method of change control, without any regulatory approval. Therefore it becomes possible to use the recent pharmaceutical sciences and engineering information throughout the life cycle of the product. QbD functions within the design space and because of this, the need to confirm the product quality by the final product test becomes unnecessary. Processes can be adapted depending on the diversity of materials used in a way to produce a product with a continuous permanent quality; processes and products can be understood very well with this quality risk management and with the help of DoE and PAT tools (5, 12, 13).

Many associations and institutions have been performing studies for the adaptation of QbD and abovementioned guidelines to the industry. One of these institutions, International Society for Pharmaceutical Engineering (ISPE), has brought forward a brand new concept focused on the 21st century's perspective for the product quality cycle called "Product Quality Lifecycle Implementation" (PQLI) in order to implement Q8 and Q9 Quality guidelines developed by ICH (14). The purpose of PQLI concept is helping the development of practical approaches to implementation of the guidelines by collecting input from industry. PQLI encloses the entire product lifecycle and consists of three strategic matters as "the principles of quality by design", "the components of pharmaceutical quality system" and "the information management and quality risk management" (Figure 1) (15, 16).

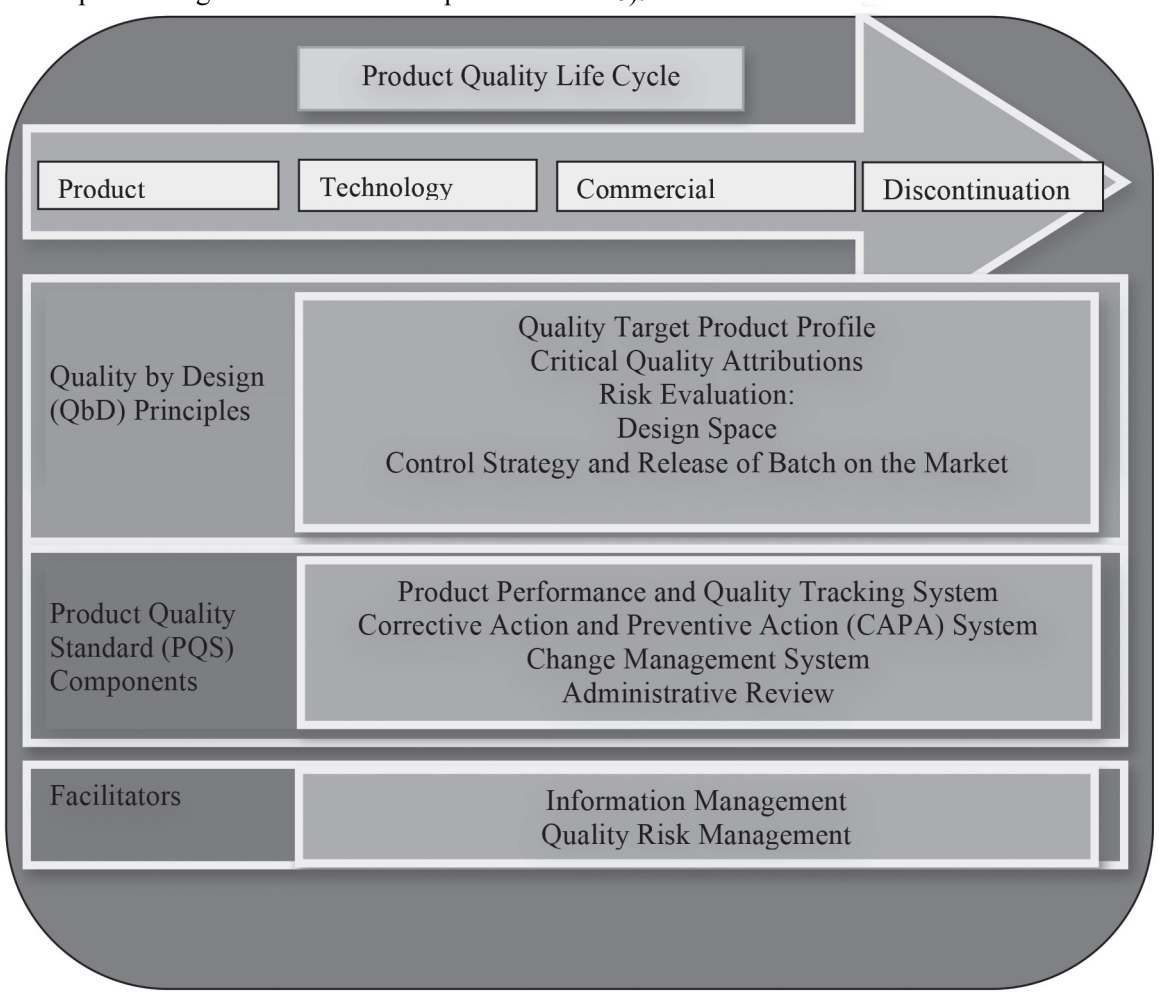

Figure 1. Product Quality Life Cycle (15, 16)

The steps of QbD(3):

- It begins with the "target product profile (TPP)" which describes the use, safety and efficacy of the product.
- "Quality target product profile", which describes the quantitative information on clinical safety and efficacy during the product development stage, is defined and used by the formulation and process personnel.
- Knowledge on the active ingredient, potential inactive substances and process operations into a knowledge space are collected. If further research is needed, risk assessment is done in order to predict the gaps in the knowledge.
- Formulations and "Critical material (quality) attributes" of the finished product, which should be controlled, are defined in order to meet the target quality product profile.
- Following the manufacturing process of the product of which the critical material attributes are determined, A Design Space or other representation of process understanding is established by combining experiences with prior knowledge for the utilization of other tools.
- A "control strategy" is created for the entire process which includes input material controls, process controls and monitoring, design spaces around single or multiple unit operations and/or finished product test. The control strategy should include the expected changes in scale. Risk assessment can be a guide to create the control strategy.
- Following this, monitorization is carried out and the process is updated to guarantee the sustainability of quality.

Quality Target Product Profile

A guideline defining the Target Product Profile (TPP) was published by FDA (17). TPP explains the product development program and drug information is given at a certain point of the development stage. It is mainly arranged according to specific parts of the directions for use and it relates the product development activities with specific issues that are requested to be included in the directions for use.

In ICH Q8 Pharmaceutical Development Guideline, QTPP also includes defining the critical attributes for the product quality, the purpose of use and route of administration in the pharmaceutical development (7). Taking into account the usage purpose and administration method is similar to TPP definition. QTPP is a summary of the product quality attributes and characteristics targeted to achieve the ideal, therefore it is aimed to guarantee the product efficacy and safety. QTPP constitutes a design base for product development and it starts with "design in mind." QTPP is a sub-branch of the Target Product Profile (TPP) published by the FDA and it focuses more on the chemical, production and control stages of development (12, 17, 18). QTPP defines quantitative targets for drug attributes (i.e. disintegration, potency, impurity, stability). It also includes specifications such as the dosage form, method of administration, package, appearance and identification (12, 13).

Critical Quality Attributes

Critical Quality Attributes (CQA) are physical, chemical, biological or microbiological attributes or characteristics which should be within the appropriate limit, range or distribution to guarantee the desired product quality, as described in ICH Q8. CQA is usually about the active ingredient, excipients, intermediates and the finished product. Finished product's critical quality attributes are created based on the quality target product profile (12).

Finished product's critical quality attributes influence the product performance within desired quality, efficacy and safety. These attributes may be those that affect specifications such as impurity, potency, stability, drug release and microbiological attributes. At the same time, they may be the active ingredient attributes that influence the product performance or reproducibility. They are widely called also as the Critical Material Attributes (CMA) (13).

Detected critical quality attributes that were found upon QTPP may be necessary to be re-assessed later; to do this, the priority listing should be done upon the initial assessment done with QTPP, by using the quality risk management tools.

After this stage, a risk analysis is performed to relate the critical process parameters and their critical quality attributes.

Critical Process Parameters

Process parameter is an attribute of the manufacturing system. Parameters are usually thought as the characteristics of the equipment or the process and manufacturing related features such as temperature and the mixing speed; whereas the attributes are thought as characteristics of the materials (i.e. melting temperature, viscosity and sterility). However, it must be noted that there aren't rigid limits between attributes and parameters.

Critical process parameter (CPP) is a process parameter, whose variability has an effect on the critical quality attribute(s), therefore it must be monitored and kept under control to guarantee the desired quality (7).

As new information is obtained and understanding of the process is developed, the CPPs can change throughout the product life cycle, new process parameters may emerge, or the acceptable range of these parameters may change due to process understanding or product improvement. All these changes may affect the manufacturing process or the design space.

Critical process parameters may vary depending on the product type, attributes of the substances in the product and target profile of the product, even if the manufacturing processes are the same. Process parameters depend on the types of equipment controls.

In QbD studies, it is critically important to determine the critical product attributes and critical process parameters defined in ICH Q8. ICH Q8 describes the critical quality attributes 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"; and critical process parameters as "process parameters whose variability has an impact on critical quality attributes and therefore should be monitored or controlled to ensure the process produces the desired quality" (7).

It is possible to assess the pharmaceutical dosage forms in two main groups as non-sterile and sterile products (Table 1). For each dosage form, critical process parameters are different. Critical process attributes during the manufacture of pharmaceutical dosage forms are displayed below.

Non-Sterile Products

Critical Quality Attributes for Solid Dosage Forms

Tablets and Film-coated tablets

CQA of tablets and film-coated tablets are summarized below (Table 2). Eventhough parameters in Table 2 are common for fundamental powder manufacturing parameters for all solid dosage forms in general, unique attributes of each pharmaceutical form are not included in this table (19-23).

Table 1. Non-sterile and sterile products

Non-Sterile Products	Sterile Products
• Solid (tablets, capsules, effervescent tablets etc.) • Liquids • Semi-solid (creams, pommades) • Two-phase systems (emulsions, suspensions)	• Powder filled • Liquids • Semi-solid (creams, pommades) • Two-phase systems (emulsions, suspensions)

Table 2. General Solid Manufacturing Operations, Process Parameters and Quality Attributes for Pharmaceutical Tablet Form (Revised from Lit. 19-23).

Pharmaceutical Operation	Sample Process Parameter	Potential Quality Attribute
Mixing	Type and shape of the mixer	Mixture uniformity
	Loading order	Particle size distribution
	Mixer loading capacity	Bulk/Tapped density
	Rotation speed and duration	Moisture content
	Mixing sticks	Flow properties
		Assay
		Impurity
Milling (granulation)	Impact/cutting/screening milling	Particle size
	Mill type and speed	Particle size distribution
	Mill type and configuration	Particle shape
	Sieve size and type	Bulk/Tapped density
	Feeding speed	Flow properties
	Fluid energy mill	Polymorphic form
	Milling nozzles	Impurity
	Nozzle pressure	
Wet granulation	In high shear granulation	Energy consumption
	Impeller, its configuration, location and speed	Mixture uniformity
		Flow
	Tank temperature	Moisture content
	Chopper speed and configuration, location and speed	Particle size and distribution
		Granule size and distribution
	Spray nozzle type and location	
	Binder liquid temperature	Granule strength and uniformity
	Binder addition duration	
	Binder addition method	Solid form
	Binder addition time and proportion	Impurity
	Mixing duration after granulation	
	Fluidized bed granulation	
	Mixing duration	
	Spray nozzle type, number, angle, configuration	
	Binder adding method	
	Binder liquid temperature	
	Binder addition time and proportion	
	Inlet air flow, volume, temperature and dew point	
	Outlet air temperature, humidity flow	
	Filter features and size	
	Shaking time	
	Product temperature	
Drying	Fluidized bed	Granule size and dispersion
	Inlet air flow, temperature, dew point,	Granule strength and uniformity
	Outlet air temperature, flow, dew	Particle size

	point Filter features Shaking frequency Product temperature Total drying duration Tray Number of trays in the oven Product amount on the tray Drying temperature and duration Airflow Inlet air dew point Vacuum/microwave Jacket temperature Condenser temperature Impeller speed Vacuum pressure values (strength) Microwave potency Electricity Energy distribution Product temperature	Flow Bulk/Tapped density Moisture content Residue solvent
Roller Compaction	Roller speed Gap settings Roll pressure Roll type Impeller auger speed	Appearance Plate particle size and shape Plate density, strength and thickness Solid form Impurity
Tablet Compression	Compression speed and force Pre-compression force Scraper type and speed Cone design, height and vibration Tablet weight and height settings Filling depth Punch penetration depth Punch set type, shape and construction material	Target weight Weight uniformity Content uniformity Hardness Height Tablet porosity Friability Appearance Moisture content Impurity Disintegration Dissolution profile Microbial limit
Coating (fluidized bed/ tank)	Product temperature Tablet pre-heating duration Spray nozzle (Type, number, angle and configuration) Individual spray gun ratio Total spray gun ratio Tank rotation speed Atomization air pressure Pattern air pressure Inlet air flow, temperature and dew point Outlet air temperature and air	Core tablet weight Appearance % weight target Film thickness Color uniformity Hardness Height Friability Assay Disintegration Impurity Microbial limit

	flow, dew point Distance from product surface to nozzles Total coating duration

Effervescent Tablets

Effervescent tablets are generally produced within conventional manufacturing methods and have the sensitivity of tablet compression; therefore they can be produced on the same equipment. Because of this, their critical quality parameters are the same. However, the difference of effervescent tablets is their manufacturing conditions (24). Environmental factors should be observed very carefully. The humidity should be below 25% and the temperature should be around 25˚C (25).

Capsules

The powder manufactured for capsule filling, pellet or tablets have the attributes of solid dosage forms in terms of critical quality attributes and process parameters. Specific differences in capsules are witnessed during the filling process. CQA for capsule filling are given below (Table 3) (26, 27).

Table 3. Capsule Pharmaceutical Form Filling Operation, Process Parameters and Quality Attributes (Revised from Lit. 26-27).

Pharmaceutical operation	Sample Process Parameter	Potential Quality Attribute
Capsule filling	Cone design, height and vibration Rotating auger filler features Vibration plate Rotating tray speed	Moisture determination Content uniformity Microbial limit Weight uniformity Disintegration Dissolution profile Assay Impurity

Table 4. Manufacturing Operations, Process Parameters and Quality Attributes for Liquid Products (Revised from Lit. 27-30).

Pharmaceutical Operation	Sample Process Parameter	Potential Quality Attribution
Mixing	Tank type and size Tank jacket temperature Impeller type and localization Mixing speed Mixing duration Homogenization method and homogenizer features Homogenization Process Duration Homogenizer Revolution Product temperature Feeding Speed of Components	Appearance Assay (Active ingredient and preservative if present) pH Density Viscosity Impurity Microbial limit
Filtration	Filter type and size Filter ΔP value Membrane filter capacity	Appearance Assay (Active ingredient and preservative if present)

	Filtration speed	pH
	Secondary filter and features	Density
	Solution Viscosity	Impurity
	Filtration duration	Microbial limit
	Pumps and their features	
Filling and sealing	Dosage system configuration and method	Appearance
	Features of filling pumps	Assay (Active ingredient and preservative if present)
		pH
	Filling speed and duration	Density
		Impurity
		Content uniformity
		Volume/Weight Controls

Table 5. Production Operations, Process Parameters and Quality Attributions for Emulsion Form (Revised from Lit. 31-33).

Pharmaceutical Operation	Sample Process Parameter	Potential Quality Attribute
Manufacturing	Granulator type and features	Humidity assignment
	Homogenizer features	Microbial limit
	Homogenization Process	Assay
	Duration	pH value
	Homogenizer rotation	Density
	Tank temperature	Viscosity
	Tank type and volume	Particle size and distribution
	Impeller type and localization	Appearance
	Feeding speed	Impurity
	Process temperatures	
	Cooling speed	
	Pumps and features	
	Rotor and stator clearance	
Filling	Packing material cleaning machine criteria (bottle, etc.)	Appearance
		Assay (Active ingredient and preservative if present)
	Filling pumps and their features	Filling weight/Volume uniformity
		Content uniformity
		pH
		Density
		Impurity

Critical Quality Attributes for Liquid Dosage Forms

The basic CQAs for liquid dosage forms are summarized below (Table 4) (27-30).

Critical Quality Attributes for Dispersed Systems

Emulsions: Emulsions can be applied via various methods such as dermal, oral, parenteral, ophthalmic or inhaler. Here, we provide the critical parameters based on manufacturing processes to for dermal and oral uses. Emulsions to be used for parenteral purposes are explained in Sterile Preparations Section 4.1.

Emulsion specific basic critical quality attributes are summarized in Table 5 (31-33).

Suspensions: Pharmaceutical suspensions are divided into three as oral, external and injectable according to their application areas. CQAs of suspension powders that are manufactured as solid powder are similar to that of general solid powder dosage forms, externally applied suspensions are similar to externally applied semi-solid forms, and injectable suspensions are similar to injection products in terms of manufacturing. However, there may be some differences due to product specific characteristics. Basic suspension specific CQAs are summarized in Table 6 (32-34).

Table 6. Production Operations, Process Parameters and Quality Attributes for Suspension Form (Revised from Lit. 32-34).

Pharmaceutical Operation	Sample Process Parameter	Potential Quality Attribute
Manufacture	Granulator type and features Tank temperature Tank type and volume Impeller type and localization Product temperature Homogenizer features Homogenization process duration Homogenizer Rotation	Moisture determination Content uniformity Microbial limit Weight uniformity Dissolution profile Assay pH value Density Viscosity Particle size and distribution Sedimentation rate and speed Appearance
Filtration	Filter type and size Filter ΔP value Integrity tests (Pre and post) Membrane filter capacity Filtration speed Secondary Filter and features Solution Viscosity Filtration duration Pumps and their features	Appearance Assay (Active ingredient and preservative if present) pH Density Impurity Microbial limit
Filling	Bottle cleaning machines criteria Filling pumps and their features	Appearance Assay (Active ingredient and preservative if present) pH Density Impurity Content uniformity Volume/Weight controls

Table 7. Manufacturing Operations, Process Parameters and Quality Attributes for Semi-Solid Products (Revised from Lit. 35-38).

Pharmaceutical Operation	Sample Process Parameter	Potential Quality Attribution
Manufacture/Mixture	Tank type and size Tank temperature Impeller type and localization Mixing speed Mixing duration Homogenizer features Homogenization Process Duration Homogenizer rotation Pumps and their features Product temperature Feeding speed	Appearance pH Density Assay (Active ingredient and preservative if present) Viscosity Particle size Impurity
Filling and sealing	Features of filling pumps Filling speed and duration	Appearance Particulate Matter Assay (active ingredient and preservative if present) Content uniformity Average weight, weight uniformity Impurity Microbial Limit

Critical Quality Attributes for Semi-solid Dosage Forms

Basic critical quality attributes for semi-solid dosage forms are given in Table 7 (35-38).

Sterile Products

Sterile preparations can be classified as solutions, suspensions, emulsions and dry powder (39-41). Since there are some criteria for the water used as excipient in sterile products and therefore it has to be assessed as a separate product, the parameters regarding water aren't included in these tables. Even though environmental factors such as air, inert gases and vapor used for technical purposes during sterile manufacturing are critical process parameters, since they require individual validations and qualifications, they are not assessed here.

Critical Quality Attributes for Sterile Powder Filling:

Aseptic powder manufacturing has different application ways and each of them has very comprehensive steps, therefore it is necessary to handle each manufacturing method individually. However, since we only aim to do a study on more general and basic applications in this publication, only the filling process of aseptic powder products is mentioned. Aseptic powder coating process will be explained in sterile liquid section; accordingly it is not mentioned here.

Aseptic powder filling specific basic critical quality attributions are summarized in Table 8 (42, 43).

Table 8. Aseptic Powder Filling Operations, Process Parameters and Quality Attributes (Revised from Lit. 42-43).

Pharmaceutical Operation	Sample Process Parameter	Potential Quality Attribute
Filling	Pump systems and features	Appearance
	Feeding speed	Assay
	Powder cone shape and features	Moisture
		Impurity
	Powder impeller shape and settings	Filling weight
		Content uniformity
	Powder flow features	
	Powder particle size	
	Filling speed	
	Structure and number of filling heads	

Critical Quality Attributes for Sterile Liquid Dosage Forms

Solutions and sterile solutions have similar critical quality attributes in terms of manufacturing process. Basic differences are applied to these two groups according to the filtration stage of the drug anufactured.

Parenteral solutions are filtered through 0.22 µm filter in order to achieve sterility and remove particulate matters, whereas other solutions are filtered through filters with larger pore sizes (39-41).

Basic CQAs for sterile liquid dosage forms are summarized in Table 9 (39-41).

Table 9. Sterile Liquid Forms Operations, Process Parameters And Quality Attributes (Revised from Lit. 39-41).

Pharmaceutical Operation	Sample Process Parameter	Potential Quality Attribute
Mixing	Homogenizer features	Appearance
	Pumps and their features	Assay (Active ingredient and preservative if present)
	Tank temperature	
	Tank type and volume	pH
	Impeller type and localization	Density
	Product temperature	Viscosity
	Feeding speed	Impurity
		Microbial limit
		Particle size
Aseptic Filtering	Filter type and size	Sterility
	Filter ΔP value	Assay (Active ingredient and preservative if present)
	Integrity tests (Pre and post)	
	Membrane filter capacity	pH
	Filtration speed	Density
	Secondary filter and features	Viscosity
	Solution viscosity	Impurity
	Filtration duration	Particle size
	Pumps and their features	
Filling and sealing	Flacon washing criteria	Appearance
	Tunnel passing speed	Sterility
	Tunnel temperature	Endotoxin limit
	Filling needle and features	Assay (Active ingredient and preservative if present)
	LAF Air flow speed and	

	features Elastic stopper sealing machine features Ampoule closing machine and features, flame settings Pumps and features	pH Density Impurity Particle size and number Ampoule leak and fracture tests Content uniformity Volume/weight controls
Sterilization by Autoclave	Vapor pressure Vapor temperature Internal air pressure Process duration Load capacity Load method	Appearance Sterility Endotoxin limit Assay (Active ingredient and preservative substance if present) pH Density Impurity

Table 10. Operations, Process Parameter And Quality Attributes For Sterile Semi-Solid Dosage Forms (Revised from Lit. 39-41, 44,45).

Pharmaceutical Operation	Sample Process Parameter	Potential Quality Attribute
Mixing	Homogenizer features Homogenization rotation Homogenization duration Pumps and their features Tank temperature Tank type and volume Impeller type and localization Mixing speed Mixing duration Product temperature Feeding speed Process temperatures Process duration Vacuum or inert gas pressure values	Appearance Assay (Active ingredient and preservative if present) pH Density Viscosity Impurity Microbial limit Particle size and distribution
Filtering	Filter type and size Filter ΔP value Integrity tests (Pre and post) Membrane filter capacity Filtration speed Secondary filter and features Solution Viscosity Filtration duration Pumps and their features	Appearance Sterility Assay (Active ingredient and preservative if present) pH Density Impurity Particle size and distribution Endotoxin limit
Filling and sealing	Flacon washing criteria Tunnel passing speed Tunnel temperature Filling needle and features LAF Air flow speed and	Appearance Sterility Endotoxin limit Assay (Active ingredient and preservative if present)

	features	pH
	Elastic stopper closing	Density
	machine features	Impurity
	Pumps and features	Particle size and number
		Ampoule leak and fracture tests
		Content uniformity
		Volume/Weight controls
		Particle size and distribution
Sterilization by Autoclave	Vapor pressure	Appearance
	Vapor temperature	Sterility
	Internal air pressure	Endotoxin limit
	Process duration	Assay (Active ingredient and
	Load capacity	preservative if present)
	Load method	pH
		Density
		Impurity
		Particle size and distribution

Critical Quality Attributes for Sterile Semi-Solid Dosage Forms

Basic CQAs for sterile semi-solid dosage forms are summarized in Table 10 (39-41, 44).

Critical Quality Attributes for Sterile Dispersed Systems

Sterile emulsion and suspension manufacturing is a very demanding process. Varying manufacturing and homogenization methods have been developed to produce a successful emulsion type preparation (for instance micro-fluidizer and two stage high pressure homogenizer). These methods have been developed to obtain more durable and easily manufactured products.

Suspensions are among the forms for which manufacturing and formulation design are most difficult. There are two simple methods used in suspension manufacturing; these are the combination of sterile carrier and powder under aseptic conditions or sterile solutions (24).

Critical quality parameters of mixing process were given under non-steril dispersed systems section (Tablo 5 –6). Critical quality attributes for dispersed systems are summarized in Table 11.

Table 11. Sterile Dispersed Systems Operations, Process Parameters and Quality Attributes

Pharmaceutical Operation	Sample Process Parameter	Potential Quality Attribute
Filtering	Filter type and size	Appearance
	Filter ΔP value	Sterility
	Integrity tests (Pre and post)	Assay (Active ingredient and
	Membrane filter capacity	preservative if present)
	Filtration speed	pH
	Secondary filter and features	Density
	Solution Viscosity	Impurity
	Filtration duration	Particle size and distribution
	Pumps and their features	Endotoxin limit
Filling and sealing	Flacon cleaning criteria	Appearance
	Tunnel passing speed	Sterility
	Tunnel temperature	Endotoxin limit
	Filling needle and features	Assay (Active ingredient and
	LAF Air flow speed and	preservative if present)

	features Elastic stopper closing machine features Pumps and features	pH Density Impurity Particle size and number Ampoule leak and fracture tests Content uniformity Volume/Weight controls Particle size and distribution
Sterilization with Autoclave	Vapor pressure Vapor temperature Internal air pressure Process duration Load capacity Load method	Appearance Sterility Endotoxin limit Assay (Active ingredient and preservative if present) pH Density Impurity Particle size and number

CONCLUSION

Design space provides high level trust for pharmaceutical quality and performance, especially when combined with control strategy and criticality assessment, and can change the licensing approaches. For the industry, it allows for more effective dialogues between the industry and authorities by offering a quite advanced and planned approach with its committed risk-based and scientific approach to product development (46).

Besides, developing the design space will provide understanding of critical and non-critical parameters as well as focus on important parameters for product quality during validation works. A more comprehensive validation acceptance criteria is obtained because the control interval where the product and process aren't affected is understood better than an interval formed empirically on its own (47).

In QbD studies, determination of critical product attributes and critical process parameters is extremely important. Critical process parameters may vary depending on the dosage form's type, properties of the components in the product and target product profile. These parameters should be monitored and controlled to assure quality (4).

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