

**ANNEX C    GUIDANCE FOR QUALITY BY DESIGN AS AN ALTERNATIVE APPROACH TO  
PROCESS VALIDATION**

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## 1. PURPOSE

This guidance document is intended to provide guidance for the submission of information and data for process validation which adopts quality by design (QbD) approach.

The guidance documents and references below should be read in conjunction with this guidance:

- Process Validation: General Principles and Practices (FDA, Jan 2011)
- Pharmaceutical Development Q8(R2) (ICH, August 2009)
- ICH Quality Risk Management Q9 (ICH, Nov 2005)
- ICH Pharmaceutical Quality System Q10 (ICH, June 2008)
- ICH Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities) Q11 (ICH, May 2012)
- ICH Quality Implementation Working Group on Q8, Q9 and Q10 Questions & Answers (R4) (ICH, Nov 2010)
- ICH Quality Implementation Working Group Points To Consider (R2) (ICH, Dec 2011)

## 2. SCOPE

This guidance applies to both chemical or biological drug products and active pharmaceutical ingredients.

## 3. GENERAL INFORMATION

FDA released “Guideline on General Principles of Process Validation” in 1987. This guideline emphasize that process validation is complete with the 3 validation lots at the commercial scale. An alternative approach to this traditional process validation is the continuous process verification, also known as life-cycle approach which is the essence of the concept of QbD.

In Aug 2009, ICH released a guideline Q8R(2) (Step 4) to guide the industry in the implementation of quality by design (QbD) in Section 3.2.P.2 (Pharmaceutical Development) for drug products as defined in the scope of Module 3 of the Common Technical Document (ICH guideline M4). QbD (ICH Q8(R2)) is defined as “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.” This is a more systematic approach to development which include, for example, incorporation of prior knowledge, results of studies using design of experiments, use of quality risk management (ICH Q9), and use of knowledge management (ICH Q10) throughout the lifecycle of the product.

Subsequently, the fourth set of Questions and Answers intended to facilitate the implementation of the Q8(R2), Q9 and Q10 Guidelines was released in Nov 2010 (Q8/Q9/Q10 Q&As (R4)). The ICH Quality IWG also released ‘Points to Consider’ covering topics relevant to the implementation of Q8(R2), Q9 and Q10, to supplement the existing Q&A in Dec 2011. Simultaneous with the development of QbD, evolution of process validation and its associated components occurs concurrently. Eventually, FDA released “Process Validation: General Principles and Practices” in Jan 2011. This guidance incorporated QbD, Process Analytical Technology (PAT), risk management and the concept of life cycle approach to process validation. This new concept emphasizes a more holistic approach to process validation.

In FDA new guidance, process validation is defined as “The collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence

that a process is capable of consistently delivering quality product. Process validation involves a series of activities taking place over the lifecycle of the product and process. This guidance describes the process validation activities in three stages.

- Stage 1 – *Process Design (PD)*: The commercial process is defined during this stage based on knowledge gained through development and scale-up activities.
- Stage 2 – *Process Qualification (PQ)*: During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.
- Stage 3 – *Continued Process Verification (CPV)*: Ongoing assurance is gained during routine production that the process remains in a state of control.

#### **4. RECOMMENDATION**

In the following sections, specific activities for each stage in the product lifecycle are described.

##### **4.1 Stage 1 - Process Design**

The objective of this stage is to provide fundamental understanding of the product and process. Product development activities are critical to the process design stage. Information such as the intended dosage form, the quality attributes, and a general manufacturing pathway affects process design. In this early stage, the functionality and limitations of commercial manufacturing equipment should be considered, as well as predicted variability at commercial scale such as different component lots, production operators, environmental conditions and measurement systems. The use of statistical experimental design such as Design of Experiment (DoE) is very useful to determine relationships, including multivariate interactions, between the variable inputs and the resulting outputs. Risk analysis tools can be used to screen potential variables for DoE studies to minimize the total number of experiments conducted while maximizing knowledge gained. The results of DOE studies can provide justification for establishing ranges of incoming component quality, equipment parameters, in-process material quality attributes, and also to establish design space.

##### **4.1.1 Design and development**

The following are some of the key points to consider in the design and development of a process.

- **Quality Target Product Profile (QTPP)** - These targets should be defined early in product and process development. Elements of QTPP include intended use in clinical setting, dosage form, route of administration, dosage strength, container closure system, pharmacokinetics and etc.
- **Critical Quality Attribute (CQA)** - CQA are those physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range or distribution to ensure the desired product quality. CQAs are derived from QTPP and scientific rationale for CQAs should be explained. They are generally associated with the drug substance, excipients, intermediates (in-process materials) and drug product (ICH). CQAs depend on the type of delivery system which will define product specific requirement such as aerodynamic properties for inhaled products, adhesion properties for transdermal patches and

etc. Some examples of product CQA for an immediate release (IR) tablet are appearance, physical attributes, dissolution, assay, content uniformity, impurity, microbial limits and etc.

- Formulation and process development – Majority of process understanding work is carried out during formulation and process development. This includes study at lab scale, pilot scale and commercial scale equipment. The preferred ingredients and its concentration are determined. Each unit operation of the entire manufacturing process are identified and it must be consistent with the manufacturing capabilities at future commercial site. Risk assessment tools as described in ICH Q9 can be used to identify potential impact of certain material attributes or process parameters to CQAs. It can be used to rank these parameters in terms of risk level based on prior knowledge and any available initial experimental data.

Below are some of the main considerations:

- a. Active Pharmaceutical Ingredient (API):  
Properties of API that potentially relevant to the manufacturing process and drug product CQA should be discussed. For examples, particle size, shape, polymorphism, solubility, flowability, compressibility, compatibility with other excipients and etc. Potential risk of API attributes on drug product CQAs should be assessed based on prior knowledge or scientific rationale. The results of the risk assessment should be discussed for each of the API attribute. If the risk is high, then further investigation is required to study the impact. Once the impact is verified, appropriate strategy to control API attribute should be put in place to ensure CQAs can be achieved. Examples of how material attributes of API affect CQAs for both chemical and biological drug can be found in ICH Q11.
- b. Formulation development:  
The chosen excipients in terms of grade/level can influence CQAs or manufacturability. Functionality of excipients, compatibility of excipients with API and other excipients should also be established. In QbD approach, understanding on how the components of the formulation affect CQAs should be discussed in greater details. The effects need to be studied either mechanistic in nature or empirical. These understanding can help to justify the choice and quality attributes of excipients. For an example, certain excipient is known to cause degradation of API based on its chemical structure. If the use of this excipient cannot be avoided, then further study is required to mitigate the risk such as by reducing the amount or the chances of contact.

During initial formulation development, detailed manufacturing process has not yet been established. Manufacturer can propose a suitable process based on prior knowledge on similar product, similar formulation and/or pre-formulation. An initial risk assessment can be performed to rate the risk based on the flexibility of the unit operation if formulation changes slightly. Risk assessment is performed based on assumptions and context. Manufacturer should provide justification on the results of initial risk assessment and which factors will be studied in the actual formulation development. After the completion of formulation development experimental studies, often performed in lab scale,

formulation risk assessment can be revised accordingly. A proposed product formula is developed and this can now proceed to process development.

c. Process development:

Critical process parameter (CPP) affects CQA and these parameters or variables should be studied based on risk assessment and statistically designed experiment. Types of risk assessment tool are described in ICH Q9. Initial risk assessment can be performed to study the impact of unit operation to CQAs. Initial list of potential critical parameters can be quite extensive, but this can be refined through experimentation. Conventional approach to study effect of process parameter one-factor-at-a-time should not be considered in QbD approach. Instead, DoE should be performed to screen potential critical parameters with reduced number of experimentation. Once CPPs are identified, more detailed DoE study usually at pilot scale can be performed to gain higher level of process understanding and to establish control strategy.

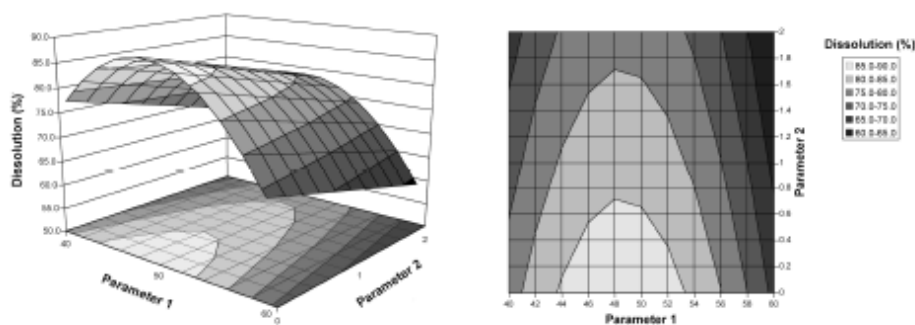
A range of process scales building towards commercial scale can be proposed based on prior knowledge or empirical experiment data. Thereafter, the effect of scale up for each of the unit operation should also be studied or discussed. Scale-up factor can be used for some equipment if properly justified. Once adequate product and process understanding are established at lab and pilot scale, the next step is to transfer this knowledge to the actual manufacturing site. Manufacturing at commercial scale may be significantly different from small scale processing. In fact, some aspects of manufacturing process can only be studied at commercial scale. Effective technology transfer to commercial scale is a critical step to the future process validation and routine manufacturing. Manufacturer may conduct partial scale process to provide more assurance of capabilities at full scale. Thereafter, validation of conformance lots can then commence to confirm the success of QbD development and scale-up.

d. Design space:

In ICH Q8(R2), It is defined 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.” Working within this space is not considered as a change and hence does not require regulatory approval. Design space can be described in terms of ranges of material attributes and process parameters, or through more complex mathematical relationships. It is generally determined through statistically designed experiment such as Design of Experiment (DoE). This enables maximum information with minimum experimental trials. Design space is only for CPP or critical material attributes that has direct impact to product CQA. It can be established for each unit operation or spans a few unit operations or the entire process.

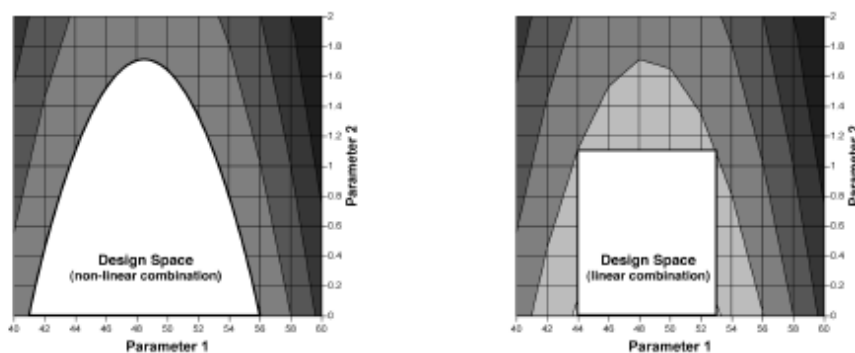
When DoE is performed to establish CPPs and/or design space, manufacturer should provide rationale for selection of DoE variables (including ranges), justification for the type of experimental design used including the power of the design, whether factors are scale-dependent, suitability of the analytical method used, results and statistical analysis of DoE data showing the statistical significance of individual factor and their interactions and predictions with relevant to scale and equipment differences. Below is an example of design space (non-linear and linear expression) of two CPPs in granulation step in relation to dissolution (extracted from ICH Q8(R2)).

**Example 1:** Response graphs for dissolution are depicted as a surface plot (Figure 1a) and a contour plot (Figure 1b). Parameters 1 and 2 are factors of a granulation operation that affect the dissolution rate of a tablet (e.g., excipient attribute, water amount, granule size.)



**Figure 1a:** Response surface plot of dissolution as a function of two parameters of a granulation operation. Dissolution above 80% is desired.

**Figure 1b:** Contour plot of dissolution from example 1a.



**Figure 1c:** Design space for granulation parameters, defined by a non-linear combination of their ranges, that delivers satisfactory dissolution (i.e., >80%).

**Figure 1d:** Design space for granulation parameters, defined by a linear combination of their ranges, that delivers satisfactory dissolution (i.e., >80%).

It is important to justify the relevance of a design space developed at small or pilot scale to the proposed production scale manufacturing process and discuss the potential risks in the scale-up operation. Design space should be verified and operational at full scale, although there is no requirement to develop a design space at the full manufacturing scale. Verification of design space should not be confused with process validation. However, it can include monitoring or testing of CQAs that are influenced by scale-dependent parameters. Factors that could trigger design space verification are change of equipment, change of manufacturing site and etc.

There is no need to run the qualification batches at the outer limits of the design space during process validation studies at commercial scale. The design space must be sufficiently explored earlier during development studies. It is encouraged to determine the edge of failure for process parameters or material attributes, but these are not essential parts of establishing a design space.

A combination of proven acceptable ranges (PARs) developed from univariate experimentation does not constitute a design space. Proven acceptable

ranges from only univariate experimentation may lack an understanding of interactions between the process parameters and/or material attributes.

Mathematical modeling is not required to develop a Design Space, but if chosen the model needs to be verified, updated and maintained. One of the methods to validate the model is through internal cross-validation techniques using the same data set. Prediction accuracy and variability due to process operation and/or analytical method should be explained. The model has to show scale and equipment independent. Design space can be updated over the lifecycle as more knowledge is gained. Operating within design space is part of a control strategy and it is not considered a change, hence post approval filing is not necessary.

#### 4.1.2 Establishing a Strategy for Process Control

The aim of process control is to control variability and it can be achieved by reducing input variation and/or adjust for input variation during manufacturing. Before that, identification of formulation and process variables are key element of life cycle approach to process validation. This includes variation at each unit operation and examples of process input variables are materials, equipments, processes, measurement system, personnel, environment and etc. Strategy to control these variables should be justified based on product and process understanding.

A robust process is able to produce product with acceptable quality despite reasonable variation in process inputs. Manufacturer should study these variables and verify control strategy during commercial production. It may be necessary to revisit the process design stage and strategy for control if the process is found to be not robust. The control strategy should be established in the master production and control records.

More advanced control strategy may include the use of process analytical technology (PAT) which can provide real time analysis and control of the output quality. PAT method is recommended but its process qualification will be different than the other process designs. PAT is often regarded as the enabler tool for QbD where it can enhance process understanding. The use of PAT provides manufacturer the opportunity for real time release without end product testing. However, implementation of real time release testing (RTRT) does not replace the review and quality control steps in releasing a batch under GMP. If RTRT is proposed in product specification, then it should be routinely used for the batch release decisions and not be substituted by end product testing when there is failure. The release of the implicated batch will only be made based on the results of the investigations. In addition, stability studies still need to be performed with the implementation of RTRT.

#### 4.2 Stage 2 – Process Qualification

The objective is to determine whether the process design is capable of reproducible commercial manufacture. It consists of two elements: (1) design of the facility and qualification of the equipment and utilities and (2) Process Performance Qualification (PPQ).

Qualification of utilities and equipment is to ensure they are suitable for their intended use and perform properly. It should include challenging the equipment and system with comparable load, intervention, stoppage and start-up during routine production. This is the pre-requisite for the commencement of PPQ.

PPQ is to confirm process design at commercial scale and it must be successfully executed before the commercial distribution of drug product. It is not typically necessary to study the entire operating range at commercial scale if sufficient assurance can be provided by process design data. However, it is expected to have higher level of sampling, additional testing and greater scrutiny in this stage. It should be continued through the process verification stage as appropriate. Consideration for the duration of the heightened sampling and monitoring period should be based on scientific justification such as prior knowledge, volume of production, process complexity and etc. The use of PAT may warrant a different PPQ approach where it focuses more on the measurement system and control loop of the measured attributes. However, new sampling techniques or new tests should not be attempted in this stage where it should be studied during process design stage. There should be no new requirements or specifications that have not been evaluated.

Before executing the validation, a Validation Master Plan (VMP) that states site validation/qualification general philosophy and approach should be defined. In the VMP, validation plan for this specific PPQ to be executed should include technical considerations to demonstrate process understanding, approach and strategy, documentation requirement and references documents. A written PPQ protocol that specifies the manufacturing conditions, controls, sampling plan, testing, and expected results must be defined and approved by appropriate department before it is being executed. Scientific rationale for the number of batches and sampling plan in PPQ should be statistically justified.

PPQ lots or sometimes called conformance lots should be manufactured under normal routine condition by the expected personnel. PPQ report should summarize data collected and data analysis, discussion on any deviations, unexpected observations, corrective actions and changes, conclusion of whether process is in a state of control. If it does not meet the pre-defined acceptance criteria, manufacturer can re-visit the process design stage to gain more understanding and confidence before repeating the PPQ. The discussion on Stage 3 of Continued Process Verification should also be included in PPQ report.

#### 4.3 Stage 3 – Continued Process Verification

The objective is to provide continual assurance that the process remains in a state of control during routine commercial production. Quality system to monitor process data, to detect any undesirable process variability and the necessary actions should be established. Data collected include process trend and quality of in-coming material, in-process material and finished product. The use of modern statistical software which enable literally instantaneous evaluation of data such as control charting and process capability indicators is recommended. These data should be statistically trended and reviewed periodically by statistician to confirm the validated state. It is recommended to use heightened sampling and testing of process parameters and quality attributes in this stage until sufficient data generated for estimation of variability. This will form the basis for establishing level and frequency of routine sampling and monitoring. Process variability should be reviewed periodically. Annual review of manufacturing data should be regarded as minimum requirement. The frequency and extent of review should be based on product/process risk considerations where more frequent review is expected for critical process parameters and critical quality attributes. Periodic review can be adjusted accordingly when sufficient reliable product and process history is demonstrated.

(ICH-PtC) CQAs and CPPs can evolve throughout the product life cycle when more product and process understanding are gained. For an example, change of manufacturing process, raw material variability and etc. As such, control strategy to ensure CQAs are met will also



evolve throughout the lifecycle. Company should file post approval variation if the change of control strategy is outside the approved design space.

## 5. REGULATORY SUBMISSION OF DOCUMENTS IN ASEAN COMMON TECHNICAL FORMAT (ACTD)

Information obtained from pharmaceutical development studies could be accommodated by the ACTD format in different ways. Below are some recommendations on how to arrange these information during regulatory submission. Applicant should clearly indicate where the different information is located for ease of reference.

For drug product, most of the product and process development information can be included in the relevant section of Part II P2. For instance, information on impact of API attributes to CQAs can be included in Part II P2.2.1. Formulation development and process development can be included in Part II P2.3 and P2.4 respectively. These include quality risk management, DoE study and basis for design space established through developmental study. However, the proposed design space at commercial scale can be included in Part II P3.2 and P3.3 as it is an element of proposed manufacturing process and control. Information on process qualification (stage 2) at commercial scale should be presented in Part II P3.4. Overall drug product control strategy including continued process verification can be included in Part II P5.6, but detailed information about input material control (i.e. Part II P4) and process control (i.e. Part II P3.3) should be included in the relevant ACTD sections.

Although the above discussion focus on pharmaceutical development Part II P2 of drug product, process validation adopting QbD approach can also be applied to API manufacturing. For API, development of synthesis process at smaller scale including selection of starting material, reagents, equipment, DoE study and basis for design space can be included in Part II S2.6. Verification of the process validation at the commercial scale can be included in Part II S2.5. Proposed design space at commercial scale should be described in Part II S2.2 and S2.4. Overall drug substance control strategy including continued process verification can be included in Part II S4.5 but detailed information about input material control (i.e. Part II S2.3) and process control (i.e. Part II S2.4) should be included in the relevant ACTD sections.

## 6. GLOSSARY

### **Critical Process Parameter (CPP):**

A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality.

### **Critical Quality Attribute (CQA):**

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.

### **Design Space:**

The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval (ICH Q8).

**Proven Acceptable Range (PAR):**

A characterised range of a process parameter for which operation within this range, while keeping other parameters constant, will result in producing a material meeting relevant quality criteria.

**Quality by Design (QbD):**

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.

**Quality Target Product Profile (QTPP):**

A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product.

**Real Time Release Testing:**

The ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically include a valid combination of measured material attributes and process controls.

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