INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

PHARMACEUTICAL DEVELOPMENT
Q8(R2)

Current *Step 4* version
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This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

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PHARMACEUTICAL DEVELOPMENT

ICH Harmonised Tripartite Guideline

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PHARMACEUTICAL DEVELOPMENT

ICH Harmonised Tripartite Guideline

Having reached *Step 4* of the ICH Process at the ICH Steering Committee meeting on 10 November 2005, this guideline is recommended for adoption to the three regulatory parties to ICH

1. INTRODUCTION

1.1 Objective of the Guideline

This guideline describes the suggested contents for the 3.2.P.2 (Pharmaceutical Development) section of a regulatory submission in the ICH M4 Common Technical Document (CTD) format.

The Pharmaceutical Development section provides an opportunity to present the knowledge gained through the application of scientific approaches and quality risk management (for definition, see ICH Q9) to the development of a product and its manufacturing process. It is first produced for the original marketing application and can be updated to support new knowledge gained over the lifecycle* of a product. The Pharmaceutical Development section is intended to provide a comprehensive understanding of the product and manufacturing process for reviewers and inspectors. The guideline also indicates areas where the demonstration of greater understanding of pharmaceutical and manufacturing sciences can create a basis for flexible regulatory approaches. The degree of regulatory flexibility is predicated on the level of relevant scientific knowledge provided.

1.2 Scope

This guideline is intended to provide guidance on the contents of 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). The guideline does not apply to contents of submissions for drug products during the clinical research stages of drug development. However, the principles in this guideline are important to consider during those stages as well. This guideline might also be appropriate for other types of products. To determine the applicability of this guideline to a particular type of product, applicants can consult with the appropriate regulatory authorities.

2. PHARMACEUTICAL DEVELOPMENT

The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product. The information and knowledge gained from pharmaceutical development studies and manufacturing experience provide scientific understanding to support the establishment of the design space*, specifications, and manufacturing controls.

Information from pharmaceutical development studies can be a basis for quality risk management. It is important to recognize that quality* cannot be tested into products;

* See Glossary for definition

i.e., quality should be built in by design. Changes in formulation and manufacturing processes during development and lifecycle management should be looked upon as opportunities to gain additional knowledge and further support establishment of the design space. Similarly, inclusion of relevant knowledge gained from experiments giving unexpected results can also be useful. Design space is proposed by the applicant and is subject to regulatory assessment and approval. 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.

The Pharmaceutical Development section should describe the knowledge that establishes that the type of dosage form selected and the formulation proposed are suitable for the intended use. This section should include sufficient information in each part to provide an understanding of the development of the drug product and its manufacturing process. Summary tables and graphs are encouraged where they add clarity and facilitate review.

At a minimum, those aspects of drug substances, excipients, container closure systems, and manufacturing processes that are critical to product quality should be determined and control strategies justified. Critical formulation attributes and process parameters are generally identified through an assessment of the extent to which their variation can have impact on the quality of the drug product.

In addition, the applicant can choose to conduct pharmaceutical development studies that can lead to an enhanced knowledge of product performance over a wider range of material attributes, processing options and process parameters. Inclusion of this additional information in this section provides an opportunity to demonstrate a higher degree of understanding of material attributes, manufacturing processes and their controls. This scientific understanding facilitates establishment of an expanded design space. In these situations, opportunities exist to develop more flexible regulatory approaches, for example, to facilitate:

- risk-based regulatory decisions (reviews and inspections);
- manufacturing process improvements, within the approved design space described in the dossier, without further regulatory review;
- reduction of post-approval submissions;
- real-time quality control, leading to a reduction of end-product release testing.

To realise this flexibility, the applicant should demonstrate an enhanced knowledge of product performance over a range of material attributes, manufacturing process options and process parameters. This understanding can be gained by application of, for example, formal experimental designs*, process analytical technology (PAT)*, and/or prior knowledge. Appropriate use of quality risk management principles can be helpful in prioritising the additional pharmaceutical development studies to collect such knowledge.

The design and conduct of pharmaceutical development studies should be consistent with their intended scientific purpose. It should be recognized that the level of

* See Glossary for definition

knowledge gained, and not the volume of data, provides the basis for science-based submissions and their regulatory evaluation.

2.1 Components of the Drug Product

2.1.1 Drug Substance

The physicochemical and biological properties of the drug substance that can influence the performance of the drug product and its manufacturability, or were specifically designed into the drug substance (e.g., solid state properties), should be identified and discussed. Examples of physicochemical and biological properties that might need to be examined include solubility, water content, particle size, crystal properties, biological activity, and permeability. These properties could be inter-related and might need to be considered in combination.

To evaluate the potential effect of drug substance physicochemical properties on the performance of the drug product, studies on drug product might be warranted. For example, the ICH *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* describes some of the circumstances in which drug product studies are recommended (e.g., Decision Tree #3 and #4 (Part 2)). This approach applies equally for the ICH *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnology/Biological Products*. The knowledge gained from the studies investigating the potential effect of drug substance properties on drug product performance can be used, as appropriate, to justify elements of the drug substance specification (3.2.S.4.5).

The compatibility of the drug substance with excipients listed in 3.2.P.1 should be evaluated. For products that contain more than one drug substance, the compatibility of the drug substances with each other should also be evaluated.

2.1.2 Excipients

The excipients chosen, their concentration, and the characteristics that can influence the drug product performance (e.g., stability, bioavailability) or manufacturability should be discussed relative to the respective function of each excipient. This should include all substances used in the manufacture of the drug product, whether they appear in the finished product or not (e.g., processing aids). Compatibility of excipients with other excipients, where relevant (for example, combination of preservatives in a dual preservative system), should be established. The ability of excipients (e.g., antioxidants, penetration enhancers, disintegrants, release controlling agents) to provide their intended functionality, and to perform throughout the intended drug product shelf life, should also be demonstrated. The information on excipient performance can be used, as appropriate, to justify the choice and quality attributes of the excipient, and to support the justification of the drug product specification (3.2.P.5.6).

Information to support the safety of excipients, when appropriate, should be cross-referenced (3.2.P.4.6).

2.2 Drug Product

2.2.1 Formulation Development

A summary should be provided describing the development of the formulation, including identification of those attributes that are critical to the quality of the drug

product, taking into consideration intended usage and route of administration. Information from formal experimental designs can be useful in identifying critical or interacting variables that might be important to ensure the quality of the drug product.

The summary should highlight the evolution of the formulation design from initial concept up to the final design. This summary should also take into consideration the choice of drug product components (e.g., the properties of the drug substance, excipients, container closure system, any relevant dosing device), the manufacturing process, and, if appropriate, knowledge gained from the development of similar drug product(s).

Any excipient ranges included in the batch formula (3.2.P.3.2) should be justified in this section of the application; this justification can often be based on the experience gained during development or manufacture.

A summary of formulations used in clinical safety and efficacy and in any relevant bioavailability or bioequivalence studies should be provided. Any changes between the proposed commercial formulation and those formulations used in pivotal clinical batches and primary stability batches should be clearly described and the rationale for the changes provided.

Information from comparative in vitro studies (e.g., dissolution) or comparative in vivo studies (e.g., bioequivalence) that links clinical formulations to the proposed commercial formulation described in 3.2.P.1 should be summarized and a cross-reference to the studies (with study numbers) should be provided. Where attempts have been made to establish an in vitro/in vivo correlation, the results of those studies, and a cross-reference to the studies (with study numbers), should be provided in this section. A successful correlation can assist in the selection of appropriate dissolution acceptance criteria, and can potentially reduce the need for further bioequivalence studies following changes to the product or its manufacturing process.

Any special design features of the drug product (e.g., tablet score line, overfill, anti-counterfeiting measure as it affects the drug product) should be identified and a rationale provided for their use.

2.2.2 Overages

In general, use of an overage of a drug substance to compensate for degradation during manufacture or a product's shelf life, or to extend shelf life, is discouraged.

Any overages in the manufacture of the drug product, whether they appear in the final formulated product or not, should be justified considering the safety and efficacy of the product. Information should be provided on the 1) amount of overage, 2) reason for the overage (e.g., to compensate for expected and documented manufacturing losses), and 3) justification for the amount of overage. The overage should be included in the amount of drug substance listed in the batch formula (3.2.P.3.2).

2.2.3 Physicochemical and Biological Properties

The physicochemical and biological properties relevant to the safety, performance or manufacturability of the drug product should be identified and discussed. This includes the physiological implications of drug substance and formulation attributes. Studies could include, for example, the development of a test for respirable fraction of an inhaled product. Similarly, information supporting the selection of dissolution vs.

disintegration testing, or other means to assure drug release, and the development and suitability of the chosen test, could be provided in this section. See also ICH *Q6A Specifications: Test Procedures And Acceptance Criteria For New Drug Substances And New Drug Products: Chemical Substances*; Decision Tree #4 (Part 3) and Decision Tree #7 (Part 1) or ICH *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnology/Biological Products*. The discussion should cross-reference any relevant stability data in 3.2.P.8.3.

2.3 Manufacturing Process Development

The selection, the control, and any improvement of the manufacturing process described in 3.2.P.3.3 (i.e., intended for commercial production batches) should be explained. It is important to consider the critical formulation attributes, together with the available manufacturing process options, in order to address the selection of the manufacturing process and confirm the appropriateness of the components. Appropriateness of the equipment used for the intended products should be discussed. Process development studies should provide the basis for process improvement, process validation, continuous process verification* (where applicable), and any process control requirements. Where appropriate, such studies should address microbiological as well as physical and chemical attributes. The knowledge gained from process development studies can be used, as appropriate, to justify the drug product specification (3.2.P.5.6).

The manufacturing process development programme or process improvement programme should identify any critical process parameters that should be monitored or controlled (e.g., granulation end point) to ensure that the product is of the desired quality.

For those products intended to be sterile an appropriate method of sterilization for the drug product and primary packaging material should be chosen and the choice justified.

Significant differences between the manufacturing processes used to produce batches for pivotal clinical trials (safety, efficacy, bioavailability, bioequivalence) or primary stability studies and the process described in 3.2.P.3.3 should be discussed. The discussion should summarise the influence of the differences on the performance, manufacturability and quality of the product. The information should be presented in a way that facilitates comparison of the processes and the corresponding batch analyses information (3.2.P.5.4). The information should include, for example, (1) the identity (e.g., batch number) and use of the batches produced (e.g., bioequivalence study batch number), (2) the manufacturing site, (3) the batch size, and (4) any significant equipment differences (e.g., different design, operating principle, size).

In order to provide flexibility for future process improvement, when describing the development of the manufacturing process, it is useful to describe measurement systems that allow monitoring of critical attributes or process end-points. Collection of process monitoring data during the development of the manufacturing process can provide useful information to enhance process understanding. The process control strategies that provide process adjustment capabilities to ensure control of all critical attributes should be described.

* See Glossary for definition

An assessment of the ability of the process to reliably produce a product of the intended quality (e.g., the performance of the manufacturing process under different operating conditions, at different scales, or with different equipment) can be provided. An understanding of process robustness* can be useful in risk assessment and risk reduction (see ICH *Q9 Quality Risk Management* glossary for definition) and to support future manufacturing and process improvement, especially in conjunction with the use of risk management tools (see ICH *Q9 Quality Risk Management*).

2.4 Container Closure System

The choice and rationale for selection of the container closure system for the commercial product (described in 3.2.P.7) should be discussed. Consideration should be given to the intended use of the drug product and the suitability of the container closure system for storage and transportation (shipping), including the storage and shipping container for bulk drug product, where appropriate.

The choice of materials for primary packaging should be justified. The discussion should describe studies performed to demonstrate the integrity of the container and closure. A possible interaction between product and container or label should be considered.

The choice of primary packaging materials should consider, e.g., choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form (including sorption to container and leaching), and safety of materials of construction. Justification for secondary packaging materials should be included, when relevant.

If a dosing device is used (e.g., dropper pipette, pen injection device, dry powder inhaler), it is important to demonstrate that a reproducible and accurate dose of the product is delivered under testing conditions which, as far as possible, simulate the use of the product.

2.5 Microbiological Attributes

Where appropriate, the microbiological attributes of the drug product should be discussed in this section (3.2.P.2.5). The discussion should include, for example:

- The rationale for performing or not performing microbial limits testing for non sterile drug products (e.g., Decision Tree #8 in ICH *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* and ICH *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnology/Biological Products)*;
- The selection and effectiveness of preservative systems in products containing antimicrobial preservative or the antimicrobial effectiveness of products that are inherently antimicrobial;
- For sterile products, the integrity of the container closure system as it relates to preventing microbial contamination.

Although chemical testing for preservative content is the attribute normally included in the drug product specification, antimicrobial preservative effectiveness should be demonstrated during development. The lowest specified concentration of antimicrobial preservative should be demonstrated to be effective in controlling micro-

* See Glossary for definition

organisms by using an antimicrobial preservative effectiveness test. The concentration used should be justified in terms of efficacy and safety, such that the minimum concentration of preservative that gives the required level of efficacy throughout the intended shelf life of the product is used. Where relevant, microbial challenge testing under testing conditions that, as far as possible, simulate patient use should be performed during development and documented in this section.

2.6 Compatibility

The compatibility of the drug product with reconstitution diluents (e.g., precipitation, stability) should be addressed to provide appropriate and supportive information for the labelling. This information should cover the recommended in-use shelf life, at the recommended storage temperature and at the likely extremes of concentration. Similarly, admixture or dilution of products prior to administration (e.g., product added to large volume infusion containers) might need to be addressed.

3. GLOSSARY

Continuous Process Verification:

An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated.

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.

Formal Experimental Design:

A structured, organized method for determining the relationship between factors affecting a process and the output of that process. Also known as "Design of Experiments".

Lifecycle:

All phases in the life of a product from the initial development through marketing until the product's discontinuation.

Process Analytical Technology (PAT):

A system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality.

Process Robustness:

Ability of a process to tolerate variability of materials and changes of the process and equipment without negative impact on quality.

Quality:

The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity (from ICH *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*).

PART II:
PHARMACEUTICAL DEVELOPMENT - ANNEX

ICH Harmonised Tripartite Guideline

Having reached *Step 4* of the ICH Process at the ICH Steering Committee meeting on 13 November 2008, this guideline is recommended for adoption to the three regulatory parties to ICH

1. INTRODUCTION

This guideline is an annex to ICH Q8 Pharmaceutical Development and provides further clarification of key concepts outlined in the core guideline. In addition, this annex describes the principles of quality by design[1] (QbD). The annex is not intended to establish new standards or to introduce new regulatory requirements; however, it shows how concepts and tools (e.g., design space[1]) outlined in the parent Q8 document could be put into practice by the applicant for all dosage forms. Where a company chooses to apply quality by design and quality risk management (ICH Q9, Quality Risk Management), linked to an appropriate pharmaceutical quality system, opportunities arise to enhance science- and risk-based regulatory approaches (see ICH Q10, Pharmaceutical Quality System).

Approaches to Pharmaceutical Development

In all cases, the product should be designed to meet patients' needs and the intended product performance. Strategies for product development vary from company to company and from product to product. The approach to, and extent of, development can also vary and should be outlined in the submission. An applicant might choose either an empirical approach or a more systematic approach to product development, or a combination of both. An illustration of the potential contrasts of these approaches is shown in Appendix 1. A more systematic approach to development (also defined as quality by design) can include, for example, incorporation of prior knowledge, results of studies using design of experiments, use of quality risk management, and use of knowledge management (see ICH Q10) throughout the lifecycle[1] of the product. Such a systematic approach can enhance achieving the desired quality of the product and help the regulators to better understand a company's strategy. Product and process understanding can be updated with the knowledge gained over the product lifecycle.

A greater understanding of the product and its manufacturing process can create a basis for more flexible regulatory approaches. The degree of regulatory flexibility is predicated on the level of relevant scientific knowledge provided in the registration application. It is the knowledge gained and submitted to the authorities, and not the volume of data collected, that forms the basis for science- and risk-based submissions and regulatory evaluations. Nevertheless, appropriate data demonstrating that this knowledge is based on sound scientific principles should be presented with each application.

Pharmaceutical development should include, at a minimum, the following elements:

[1] See glossary

- Defining the quality target product profile[1] (QTPP) as it relates to quality, safety and efficacy, considering e.g., the route of administration, dosage form, bioavailability, strength, and stability;
- Identifying potential critical quality attributes[1] (CQAs) of the drug product, so that those product characteristics having an impact on product quality can be studied and controlled;
- Determining the critical quality attributes of the drug substance, excipients etc., and selecting the type and amount of excipients to deliver drug product of the desired quality[1];
- Selecting an appropriate manufacturing process ;
- Defining a control strategy[1].

An enhanced, quality by design approach to product development would additionally include the following elements:

- A systematic evaluation, understanding and refining of the formulation and manufacturing process, including;
    - Identifying, through e.g., prior knowledge, experimentation, and risk assessment, the material attributes and process parameters that can have an effect on product CQAs;
    - Determining the functional relationships that link material attributes and process parameters to product CQAs;
- Using the enhanced product and process understanding in combination with quality risk management to establish an appropriate control strategy which can, for example, include a proposal for a design space(s) and/or real-time release testing[1].

As a result, this more systematic approach could facilitate continual improvement and innovation throughout the product lifecycle (See ICH Q10).

2. ELEMENTS OF PHARMACEUTICAL DEVELOPMENT

The section that follows elaborates on possible approaches to gaining a more systematic, enhanced understanding of the product and process under development. The examples given are purely illustrative and are not intended to create new regulatory requirements.

2.1 Quality Target Product Profile

The quality target product profile forms the basis of design for the development of the product. Considerations for the quality target product profile could include:

- Intended use in clinical setting, route of administration, dosage form, delivery systems;
- Dosage strength(s);
- Container closure system;

[1] See glossary

- Therapeutic moiety release or delivery and attributes affecting pharmacokinetic characteristics (e.g., dissolution, aerodynamic performance) appropriate to the drug product dosage form being developed;
- Drug product quality criteria (e.g., sterility, purity, stability and drug release) appropriate for the intended marketed product.

2.2 Critical Quality Attributes

A CQA is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. CQAs are generally associated with the drug substance, excipients, intermediates (in-process materials) and drug product.

CQAs of solid oral dosage forms are typically those aspects affecting product purity, strength, drug release and stability. CQAs for other delivery systems can additionally include more product specific aspects, such as aerodynamic properties for inhaled products, sterility for parenterals, and adhesion properties for transdermal patches. For drug substances, raw materials and intermediates, the CQAs can additionally include those properties (e.g., particle size distribution, bulk density) that affect drug product CQAs.

Potential drug product CQAs derived from the quality target product profile and/or prior knowledge are used to guide the product and process development. The list of potential CQAs can be modified when the formulation and manufacturing process are selected and as product knowledge and process understanding increase. Quality risk management can be used to prioritize the list of potential CQAs for subsequent evaluation. Relevant CQAs can be identified by an iterative process of quality risk management and experimentation that assesses the extent to which their variation can have an impact on the quality of the drug product.

2.3 Risk Assessment: Linking Material Attributes and Process Parameters to Drug Product CQAs

Risk assessment is a valuable science-based process used in quality risk management (see ICH Q9) that can aid in identifying which material attributes and process parameters potentially have an effect on product CQAs. Risk assessment is typically performed early in the pharmaceutical development process and is repeated as more information becomes available and greater knowledge is obtained.

Risk assessment tools can be used to identify and rank parameters (e.g., process, equipment, input materials) with potential to have an impact on product quality, based on prior knowledge and initial experimental data. For an illustrative example, see Appendix 2. The initial list of potential parameters can be quite extensive, but can be modified and prioritized by further studies (e.g., through a combination of design of experiments, mechanistic models). The list can be refined further through experimentation to determine the significance of individual variables and potential interactions. Once the significant parameters are identified, they can be further studied (e.g., through a combination of design of experiments, mathematical models, or studies that lead to mechanistic understanding) to achieve a higher level of process understanding.

2.4 Design Space

The relationship between the process inputs (material attributes and process parameters) and the critical quality attributes can be described in the design space (see examples in Appendix 2).

2.4.1 Selection of Variables

The risk assessment and process development experiments described in Section 2.3 can lead to an understanding of the linkage and effect of process parameters and material attributes on product CQAs, and also help identify the variables and their ranges within which consistent quality can be achieved. These process parameters and material attributes can thus be selected for inclusion in the design space.

A description should be provided in the application of the process parameters and material attributes considered for the design space, those that were included, and their effect on product quality. The rationale for inclusion in the design space should be presented. In some cases it is helpful to provide also the rationale as to why some parameters were excluded. Knowledge gained from studies should be described in the submission. Process parameters and material attributes that were not varied through development should be highlighted.

2.4.2 Describing a Design Space in a Submission

A design space can be described in terms of ranges of material attributes and process parameters, or through more complex mathematical relationships. It is possible to describe a design space as a time dependent function (e.g., temperature and pressure cycle of a lyophilisation cycle), or as a combination of variables such as components of a multivariate model. Scaling factors can also be included if the design space is intended to span multiple operational scales. Analysis of historical data can contribute to the establishment of a design space. Regardless of how a design space is developed, it is expected that operation within the design space will result in a product meeting the defined quality.

Examples of different potential approaches to presentation of a design space are presented in Appendix 2.

2.4.3 Unit Operation Design Space(s)

The applicant can choose to establish independent design spaces for one or more unit operations, or to establish a single design space that spans multiple operations. While a separate design space for each unit operation is often simpler to develop, a design space that spans the entire process can provide more operational flexibility. For example, in the case of a drug product that undergoes degradation in solution before lyophilisation, the design space to control the extent of degradation (e.g., concentration, time, temperature) could be expressed for each unit operation or as a sum over all unit operations.

2.4.4 Relationship of Design Space to Scale and Equipment

When describing a design space, the applicant should consider the type of operational flexibility desired. A design space can be developed at any scale. The applicant should 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.

If the applicant proposes the design space to be applicable to multiple operational scales, the design space should be described in terms of relevant scale-independent parameters. For example, if a product was determined to be shear sensitive in a mixing operation, the design space could include shear rate, rather than agitation rate. Dimensionless numbers and/or models for scaling can be included as part of the design space description.

2.4.5 Design Space Versus Proven Acceptable Ranges

A combination of proven acceptable ranges[1] does not constitute a design space. However, proven acceptable ranges based on univariate experimentation can provide useful knowledge about the process.

2.4.6 Design Space and Edge of Failure

It can be helpful to determine the edge of failure for process parameters or material attributes, beyond which the relevant quality attributes cannot be met. However, determining the edge of failure or demonstrating failure modes are not essential parts of establishing a design space.

2.5 Control Strategy

A control strategy is designed to ensure that a product of required quality will be produced consistently. The elements of the control strategy discussed in Section P.2 of the dossier should describe and justify how in-process controls and the controls of input materials (drug substance and excipients), intermediates (in-process materials), container closure system, and drug products contribute to the final product quality. These controls should be based on product, formulation and process understanding and should include, at a minimum, control of the critical process parameters[1] and material attributes.

A comprehensive pharmaceutical development approach will generate process and product understanding and identify sources of variability. Sources of variability that can impact product quality should be identified, appropriately understood, and subsequently controlled. Understanding sources of variability and their impact on downstream processes or processing, in-process materials, and drug product quality can provide an opportunity to shift controls upstream and minimise the need for end product testing. Product and process understanding, in combination with quality risk management (see ICH Q9), will support the control of the process such that the variability (e.g., of raw materials) can be compensated for in an adaptable manner to deliver consistent product quality.

This process understanding can enable an alternative manufacturing paradigm where the variability of input materials could be less tightly constrained. Instead it can be possible to design an adaptive process step (a step that is responsive to the input materials) with appropriate process control to ensure consistent product quality.

Enhanced understanding of product performance can justify the use of alternative approaches to determine that the material is meeting its quality attributes. The use of such alternatives could support real time release testing. For example, disintegration could serve as a surrogate for dissolution for fast-disintegrating solid forms with highly soluble drug substances. Unit dose uniformity performed in-process (e.g., using

[1] See glossary

weight variation coupled with near infrared (NIR) assay) can enable real time release testing and provide an increased level of quality assurance compared to the traditional end-product testing using compendial content uniformity standards. Real time release testing can replace end product testing, but does not replace the review and quality control steps called for under GMP to release the batch.

A control strategy can include, but is not limited to, the following:

- Control of input material attributes (e.g., drug substance, excipients, primary packaging materials) based on an understanding of their impact on processability or product quality;
- Product specification(s);
- Controls for unit operations that have an impact on downstream processing or product quality (e.g., the impact of drying on degradation, particle size distribution of the granulate on dissolution);
- In-process or real-time release testing in lieu of end-product testing (e.g. measurement and control of CQAs during processing);
- A monitoring program (e.g., full product testing at regular intervals) for verifying multivariate prediction models.

A control strategy can include different elements. For example, one element of the control strategy could rely on end-product testing, whereas another could depend on real-time release testing. The rationale for using these alternative approaches should be described in the submission.

Adoption of the principles in this guideline can support the justification of alternative approaches to the setting of specification attributes and acceptance criteria as described in Q6A and Q6B.

2.6 Product Lifecycle Management and Continual Improvement

Throughout the product lifecycle, companies have opportunities to evaluate innovative approaches to improve product quality (see ICH Q10).

Process performance can be monitored to ensure that it is working as anticipated to deliver product quality attributes as predicted by the design space. This monitoring could include trend analysis of the manufacturing process as additional experience is gained during routine manufacture. For certain design spaces using mathematical models, periodic maintenance could be useful to ensure the model's performance. The model maintenance is an example of activity that can be managed within a company's own internal quality system provided the design space is unchanged.

Expansion, reduction or redefinition of the design space could be desired upon gaining additional process knowledge. Change of design space is subject to regional requirements.

3. SUBMISSION OF PHARMACEUTICAL DEVELOPMENT AND RELATED INFORMATION IN COMMON TECHNICAL DOCUMENTS (CTD) FORMAT

Pharmaceutical development information is submitted in Section P.2 of the CTD. Other information resulting from pharmaceutical development studies could be accommodated by the CTD format in a number of different ways and some specific

suggestions are provided below. However, the applicant should clearly indicate where the different information is located. In addition to what is submitted in the application, certain aspects (e.g., product lifecycle management, continual improvement) of this guideline are handled under the applicant's pharmaceutical quality system (see ICH Q10).

3.1 Quality Risk Management and Product and Process Development

Quality risk management can be used at different stages during product and process development and manufacturing implementation. The assessments used to guide and justify development decisions can be included in the relevant sections of P.2. For example, risk analyses and functional relationships linking material attributes and process parameters to product CQAs can be included in P.2.1, P.2.2, and P.2.3. Risk analyses linking the design of the manufacturing process to product quality can be included in P.2.3.

3.2 Design Space

As an element of the proposed manufacturing process, the design space(s) can be described in the section of the application that includes the description of the manufacturing process and process controls (P.3.3). If appropriate, additional information can be provided in the section of the application that addresses the controls of critical steps and intermediates (P.3.4). The product and manufacturing process development sections of the application (P.2.1, P.2.2, and P.2.3) are appropriate places to summarise and describe product and process development studies that provide the basis for the design space(s). The relationship of the design space(s) to the overall control strategy can be discussed in the section of the application that includes the justification of the drug product specification (P.5.6).

3.3 Control Strategy

The section of the application that includes the justification of the drug product specification (P.5.6) is a good place to summarise the overall drug product control strategy. However, detailed information about input material controls and process controls should still be provided in the appropriate CTD format sections (e.g., drug substance section (S), control of excipients (P.4), description of manufacturing process and process controls (P.3.3), controls of critical steps and intermediates (P.3.4)).

3.4 Drug Substance Related Information

If drug substance CQAs have the potential to affect the CQAs or manufacturing process of the drug product, some discussion of drug substance CQAs can be appropriate in the pharmaceutical development section of the application (e.g., P.2.1).

4. GLOSSARY

Control Strategy:

A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. (ICH Q10)

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).

Lifecycle:

All phases in the life of a product from the initial development through marketing until the product's discontinuation (ICH Q8).

Proven Acceptable Range:

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:

The suitability of either a drug substance or a drug product for its intended use. This term includes such attributes as the identity, strength, and purity (ICH Q6A).

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.

Appendix 1. Differing Approaches to Pharmaceutical Development

The following table has been developed to illustrate some potential contrasts between what might be considered a minimal approach and an enhanced, quality by design approach regarding different aspects of pharmaceutical development and lifecycle management. The comparisons are shown merely to aid in the understanding of a range of potential approaches to pharmaceutical development and should not be considered to be all-encompassing. The table is not intended to specifically define the only approach a company could choose to follow. In the enhanced approach, establishing a design space or using real time release testing is not necesserily expected. Current practices in the pharmaceutical industry vary and typically lie between the two approaches presented in the table.

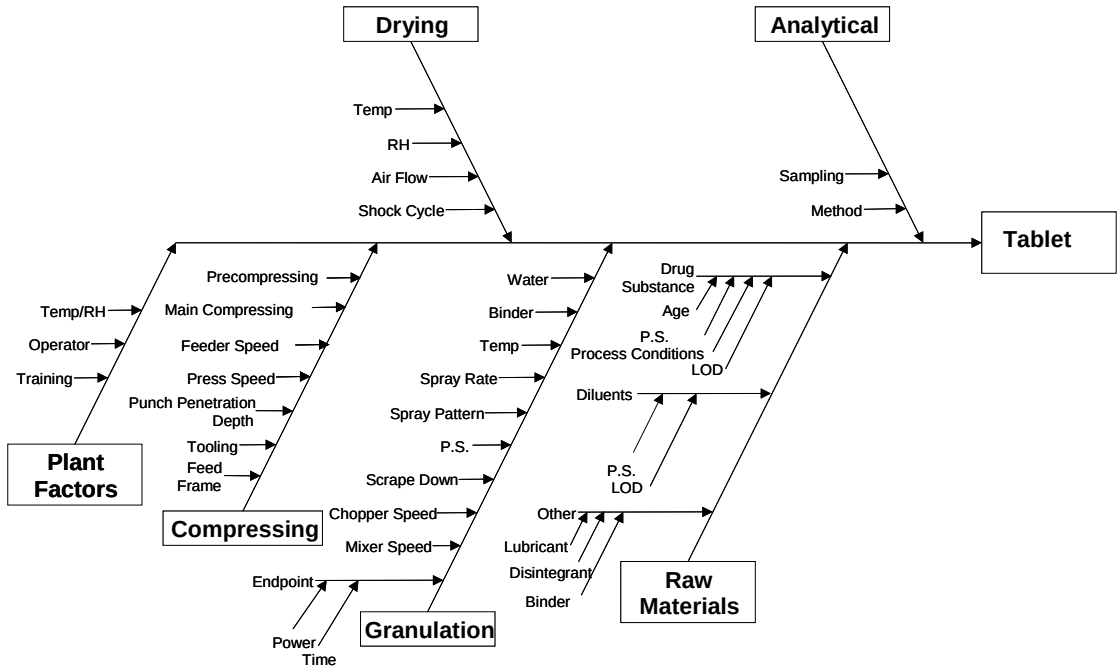
Aspect	Minimal Approaches	Enhanced, Quality by Design Approaches
Overall Pharmaceutical Development	• Mainly empirical • Developmental research often conducted one variable at a time	• Systematic, relating mechanistic understanding of material attributes and process parameters to drug product CQAs • Multivariate experiments to understand product and process • Establishment of design space • PAT tools utilised
Manufacturing Process	• Fixed • Validation primarily based on initial full-scale batches • Focus on optimisation and reproducibility	• Adjustable within design space • Lifecycle approach to validation and, ideally, continuous process verification • Focus on control strategy and robustness • Use of statistical process control methods
Process Controls	• In-process tests primarily for go/no go decisions • Off-line analysis	• PAT tools utilised with appropriate feed forward and feedback controls • Process operations tracked and trended to support continual improvement efforts post-approval
Product Specifications	• Primary means of control • Based on batch data available at time of registration	• Part of the overall quality control strategy • Based on desired product performance with relevant supportive data
Control Strategy	• Drug product quality controlled primarily by intermediates (in-process materials) and end product testing	• Drug product quality ensured by risk-based control strategy for well understood product and process • Quality controls shifted upstream, with the possibility of real-time release testing or reduced end-product testing
Lifecycle Management	• Reactive (i.e., problem solving and corrective action)	• Preventive action • Continual improvement facilitated

Appendix 2. Illustrative Examples

A. Use of a risk assessment tool.

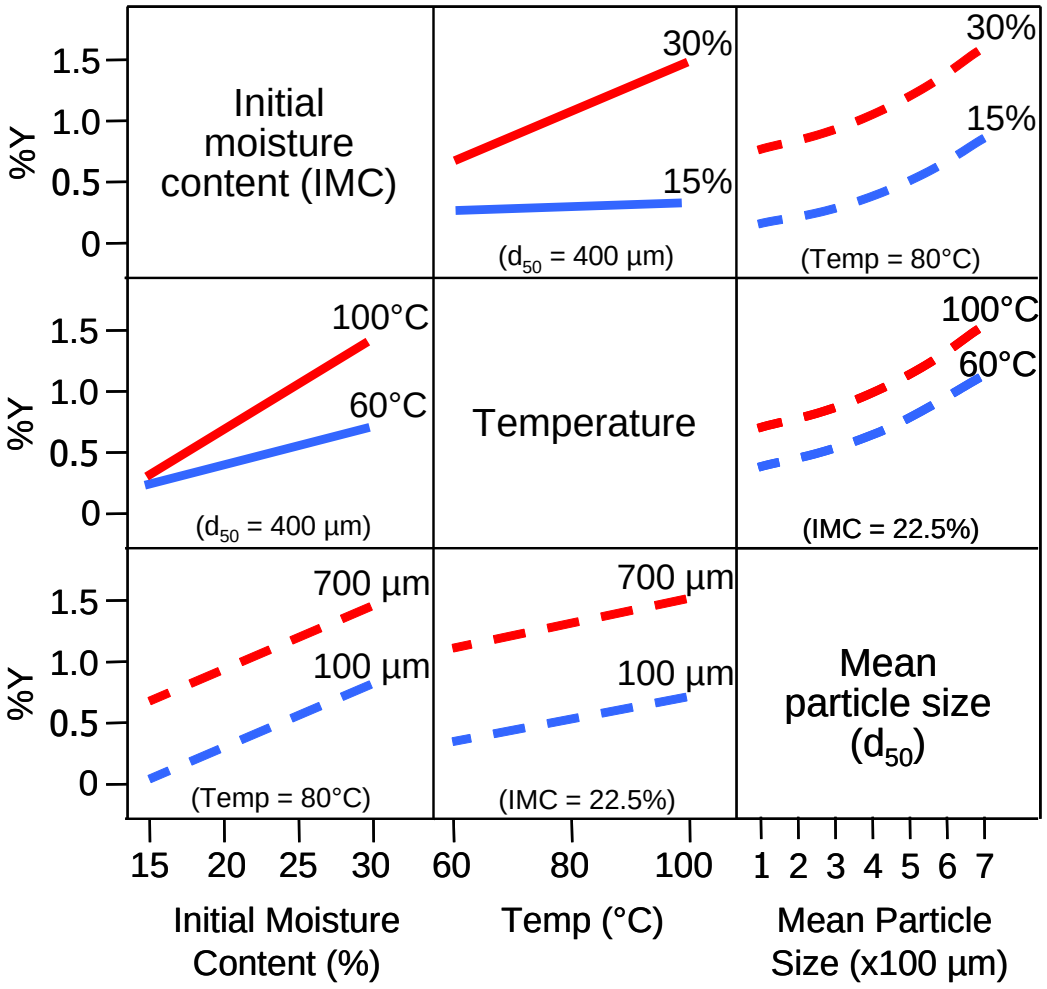
For example, a cross-functional team of experts could work together to develop an Ishikawa (fishbone) diagram that identifies potential variables which can have an impact on the desired quality attribute. The team could then rank the variables based on probability, severity, and detectability using failure mode effects analysis (FMEA) or similar tools based on prior knowledge and initial experimental data. Design of experiments or other experimental approaches could then be used to evaluate the impact of the higher ranked variables, to gain greater understanding of the process, and to develop a proper control strategy.

Ishikawa Diagram



B. Depiction of interactions

The figure below depicts the presence or absence of interactions among three process parameters on the level of degradation product Y. The figure shows a series of two-dimensional plots showing the effect of interactions among three process parameters (initial moisture content, temperature, mean particle size) of the drying operation of a granulate (drug product intermediate) on degradation product Y. The relative slopes of the lines or curves within a plot indicate if interaction is present. In this example, initial moisture content and temperature are interacting; but initial moisture content and mean particle size are not, nor are temperature and mean particle size.



C. Presentations of design space

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.)

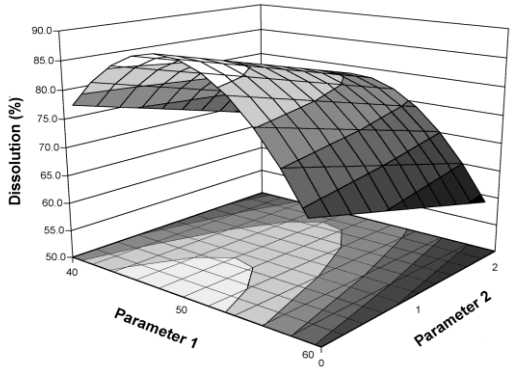


Figure 1a: Response surface plot of dissolution as a function of two parameters of a granulation operation. Dissolution above 80% is desired.

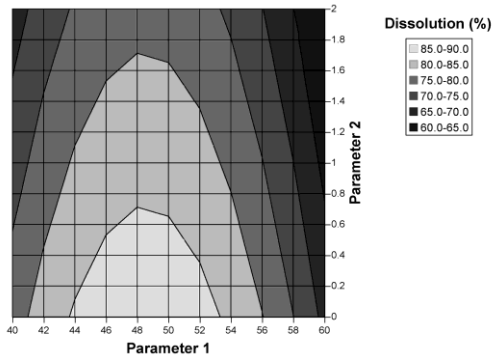


Figure 1b: Contour plot of dissolution from example 1a.

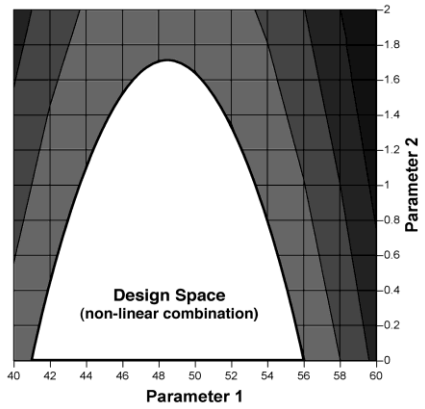


Figure 1c: Design space for granulation parameters, defined by a non-linear combination of their ranges, that delivers satisfactory dissolution (i.e., >80%).

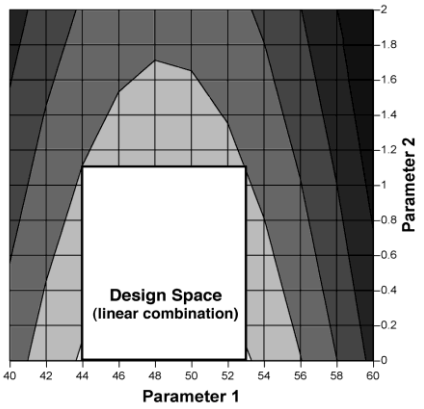


Figure 1d: Design space for granulation parameters, defined by a linear combination of their ranges, that delivers satisfactory dissolution (i.e., >80%).

Two examples are given of potential design spaces. In Figure 1c, the design space is defined by a non-linear combination of parameter ranges that delivers the dissolution critical quality attribute. In this example, the design space is expressed by the response surface equation resolved at the limit for satisfactory response (i.e.,80% dissolution). The acceptable range of one parameter is dependent on the value of the other. For example:

- *If Parameter 1 has a value of 46, then Parameter 2 has a range of 0 and 1.5*
- *If Parameter 2 has a value of 0.8, then Parameter 1 has a range of 43 and 54*

The approach in Figure 1c allows the maximum range of operation to achieve the desired dissolution rate. In Figure 1d, the design space is defined as a smaller range, based on a linear combination of parameters.

- *Parameter 1 has a range of 44 and 53*
- *Parameter 2 has a range of 0 and 1.1*

While the approach in Figure 1d is more limiting, the applicant may prefer it for operational simplicity.

This example discusses only two parameters and thus can readily be presented graphically. When multiple parameters are involved, the design space can be presented for two parameters, in a manner similar to the examples shown above, at different values (e.g., high, middle, low) within the range of the third parameter, the fourth parameter, and so on. Alternatively, the design space can be explained mathematically through equations describing relationships between parameters for successful operation.

Example 2: Design space determined from the common region of successful operating ranges for multiple CQAs. The relations of two CQAs, i.e., tablet friability and dissolution, to two process parameters of a granulation operation are shown in Figures 2a and 2b. 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 2c shows the overlap of these regions and the maximum ranges of the proposed design space. The applicant can elect to use the entire region as the design space, or some subset thereof.

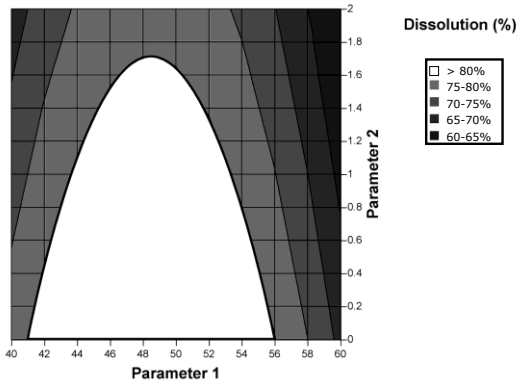


Figure 2a: Contour plot of dissolution as a function of Parameters 1 and 2.

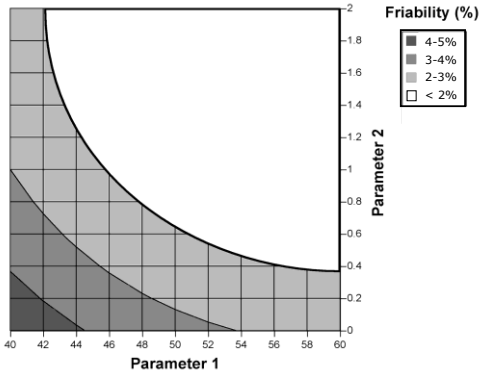


Figure 2b: Contour plot of friability as a function of Parameters 1 and 2.

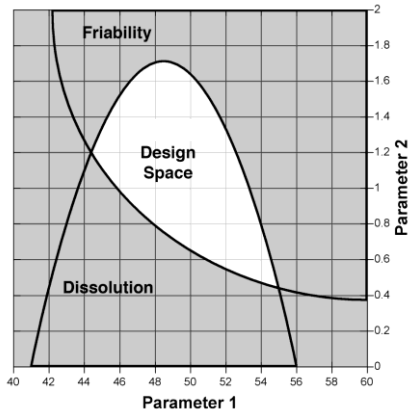


Figure 2c: Proposed design space, comprised of the overlap region of ranges for friability and or dissolution.

Example 3: The design space for a drying operation that is dependent upon the path of temperature and/or pressure over time. The end point for moisture content is 1-2%. Operating above the upper limit of the design space can cause excessive impurity formation, while operating below the lower limit of the design space can result in excessive particle attrition.