MHRA
Regulating Medicines and Medical Devices

Prior knowledge in product development/design

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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. (EU - Note for guidance on Development Pharmaceutics (CPMP/QWP/155/96))

ICH Q8 – Pharmaceutical Development

Q8: Pharmaceutical Development (May 2006)

Q8 (R1): Pharmaceutical Development Revision/Annex (November 2008)

Q8 (R2): Pharmaceutical Development – editorial corrections (June 09)

Quality by design (Q8R):

> A more systematic approach to development may include, for example, incorporation of ***prior knowledge***, results of experimental studies using *design of experiments or multivariate data analysis*, establishment of a control strategy, *use of quality risk management***,** and *use of knowledge management* (see ICH Q10) throughout the *lifecycle* of the product.

Pharmaceutical Development is a dynamic, not a static process: *lifecycle*, *continual improvement*

ICH Q8 Pharmaceutical Development

Part I: Pharmaceutical Development

1. Introduction

1.1. Objective of the Guideline

1.2. Scope

2. Pharmaceutical development

2.1. Components of the drug product

2.1.1. Drug Substance

2.1.2. Excipients

2.2. Drug product

2.2.1. Formulation development

2.2.2. Overages

2.2.3. Physicochemical and biological properties

2.3. Manufacturing process development

2.4. Container closure system

2.5. Microbiological Attributes

2.6. Compatibility

3. Glossary

ICH Q8 Pharmaceutical Development

Part II: Pharmaceutical Development – Annex

1. Introduction

2. Elements of pharmaceutical development

2.1. *Quality target product profile*

2.2. Critical quality attributes

2.3. Risk assessment: linking material attributes and process parameters to drug product CQAs

2.4. Design space

2.4.1. Selection of variables

2.4.2. Describing a design space in a submission

2.4.3. Unit operation design space(s)

2.4.4. Relationship of design space to scale and equipment

2.4.5. Design space versus proven acceptable ranges

2.4.6. Design space and edge of failure

2.5. Control strategy

2.6. Product lifecycle management and continual improvement

ICH Q8 Pharmaceutical Development

Part II:Pharmaceutical development - Annex (continued)

3. Submission of pharmaceutical development and related information in common technical documents (CTD) format

3.1. Quality risk management and product and process development
3.2. Design space
3.3. Control strategy
3.4. Drug substance related information

Frequency of use of terms: -

Knowledge – 24
Prior knowledge - 6

Product development/design

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.

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

- *Defining the quality target product profile (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 (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;*
- Selecting an appropriate manufacturing process ;
- Defining a control strategy

Formulation Development Activities

	ICH Q8(R2) – Pharmaceutical Development Related Activities	ICH Q9 – QRM Related Activities	ICH Q10 – PQS Related Integrated Activities
Quality Target Product Profile (QTPP)	• Clinical and non-clinical studies on drug substance: bioavailability, PK/PD, and safety	• Informal and/or formal risk assessment to evaluate patient needs and potential medication risks	• Knowledge Management / Prior Knowledge (relevant information to support the understanding, risk assessment and scope of DOE) - Laboratory note book documentation - Development report - Etc…
Pre-Formulation Studies	• Characterization of drug substance (physical properties) • Chemical stability of drug substance, degradation and potential formulation interactions • Development of analytical tests	• Determine failure modes and risk factors for drug substance physical and chemical stability	
Formulation Screening	• Excipient compatibility • Dissolution method development • Screening DOEs	• Determine failure modes and risk factors for excipient interactions	
Formulation Optimization and Selection	• Excipient and drug substance material property & characterization • DOEs for excipient amounts • Stability of drug product and storage conditions • Develop IVIVC relationships	• Opportunities for formal risk assessment	

From ICH Quality IWG Workshop
Talinn (6/10) and Washington (10/10)

http://www.ich.org/products/guidelines/quality/training-programme-for-q8q9q10.html

ICH Q8: Approaches to Pharmaceutical Development

MHRA

Minimal approach (traditional)

- Empirical development
- One variable at the time
- Fixed manufacturing process
- Focus on reproducibility
- Off-line analysis
- Quality assurance by testing
- Reactive lifecycle management (corrective actions)

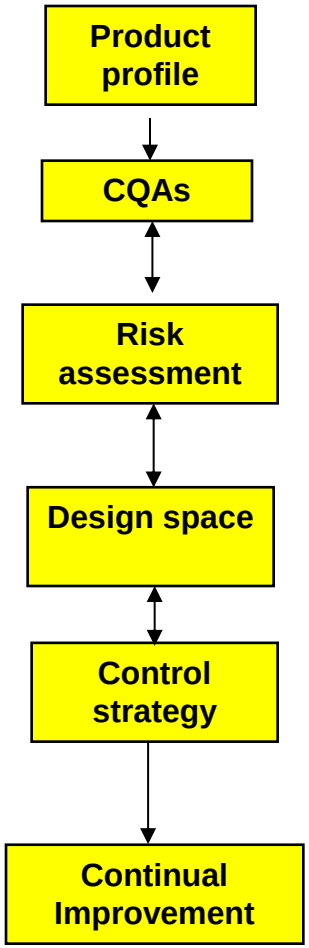
Enhanced, QbD, approach (*)

- Systematic approach to development
- Multivariate experiments, DoE
- Manufacturing process (and quantitative formulation) adjustable within the design space
- Focus on control strategy and robustness of the process
- PAT tools used for feed forward and feed back process control
- Risk based control strategy & potentially Real Time Release
- Preventive lifecycle management and continuous improvement

The product should be designed to meet patients' and the intended product performance.

(*) Optional approach. Parts may be applied.

Example ICH Q8(R2) *Enhanced* Approach



- Target the product profile
- Determine critical quality attributes (CQAs)
- Link raw material attributes and process parameters to CQAs and perform risk assessment (identify what is critical)
- Develop a design space
- Design and implement a control strategy
- Manage product lifecycle, including continual improvement

Product development/design

2. Elements of pharmaceutical development

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 (patient population), route of administration, dosage form, delivery systems;
- Dosage strength(s);
- Container closure system;
- 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.

Extent and therefore the potential role of **prior knowledge** will depend upon the nature of the submission

- New drug substance
- Existing drug substance (Generic)
- Extension – new pharmaceutical form
- Variation to existing product

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.

Illustration : QTPP and CQAs

QTPP

Dosage form and strength	Immediate release tablet containing 30 mg of active ingredient.
Specifications to assure safety and efficacy during shelf-life	Assay, Uniformity of Dosage Unit (content uniformity) and dissolution.
Description and hardness	Robust tablet able to withstand transport and handling.
Appearance	Film-coated tablet with a suitable size to aid patient acceptability and compliance. Total tablet weight containing 30 mg of active ingredient is 100 mg with a diameter of 6 mm.

CQAs derived using Prior Knowledge (e.g. previous experience of developing tablets)

CQAs may be ranked using quality risk assessment.

Drug Product CQAs

- Assay
- Content Uniformity
- Dissolution
- Tablet Mechanical Strength

Product development/design

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

e.g. solubility, water content, particle size, crystal properties, biological activity, and permeability.

To evaluate the potential effect of drug substance physicochemical properties on the performance of the drug product, studies on drug product might be warranted.

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.

Approach applies equally for the ICH *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnology/Biological Products*.

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.

Compatibility of the drug substance with excipients should be evaluated and if appopriate other drug substances in the formulation.

Prior knowledge

Will largely depend upon nature of submission.

Experience with similar drug substances/formulations

Product development/design

2.1.2. Excipients

Concentration, and the characteristics (functionality) that can influence the drug product performance (e.g., stability, bioavailability) or manufacturability should be discussed relative to the respective function of each excipient, including processing aids.

Compatibility should be established and the ability of the excipients to provide their intended functionality, and to perform throughout the intended drug product shelf life (e.g. preservatives, antioxidants), 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).

Prior knowledge

Material attributes

Typical concentrations/experience with similar formulations

Manufacturability

Information concerning safety (paediatric use)

Specifications – Monograph e.g. Ph. Eur.,

Elemental impurities

Product development/design

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).

Link to formulations used in clinical safety and efficacy and in any relevant bioavailability or bioequivalence studies.

Prior knowledge

Development of similar products

Dosage forms – general Pharmacopoeial monographs

Product development/design

2.4. Container closure system

The choice and rationale for selection of the container closure system for the commercial product 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.

Prior knowledge

Protective properties (material specifications)

Single dose/multi-dose

Integrity of container closure system – sterile products

Monograph requirements

Experience with similar products