Implementation of ICH Q8, Q9, Q10

Workshop A
Design Space (DS)

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

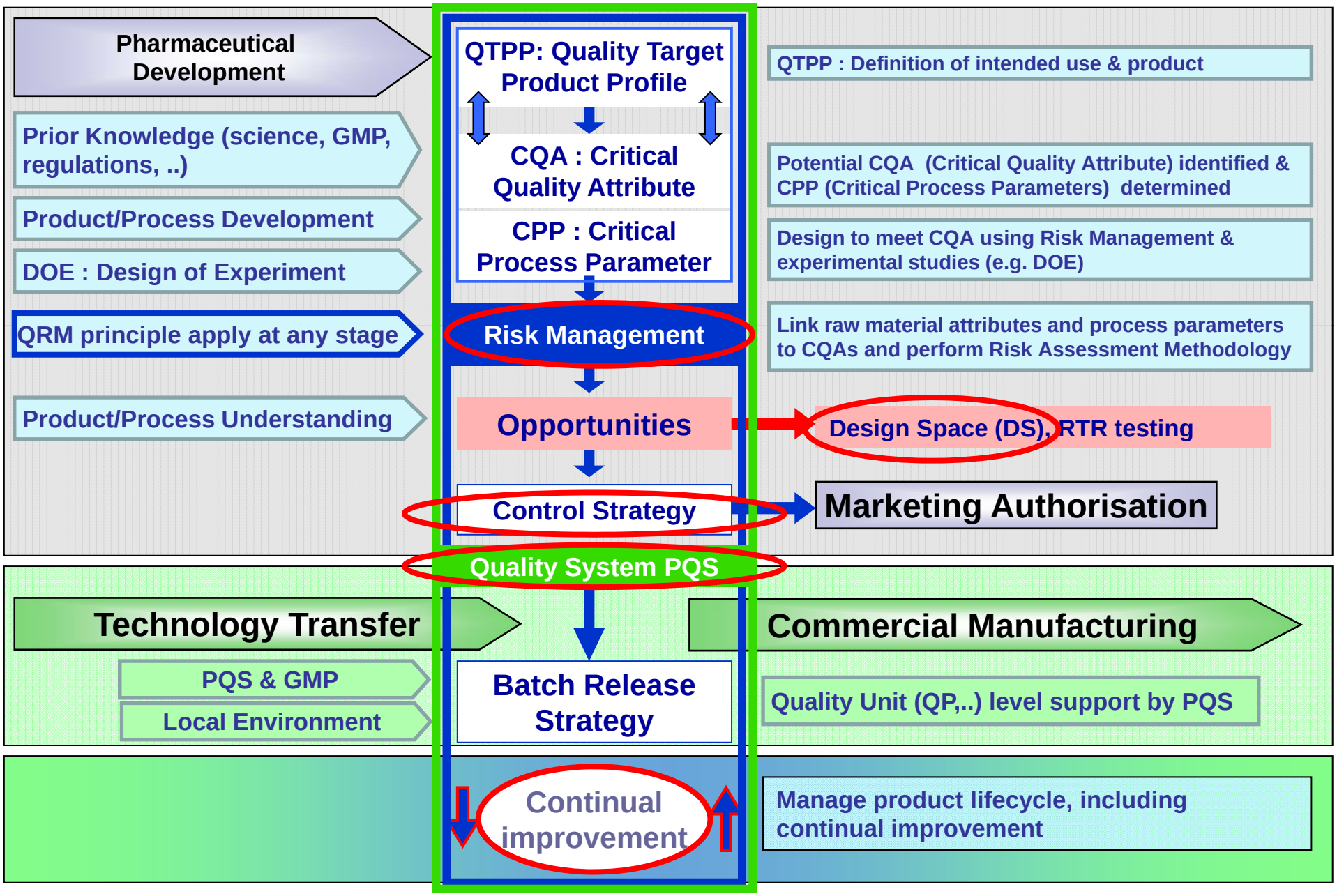
Disclaimer

The information within this presentation is based on the ICH Q-IWG members expertise and experience, and represents the views of the ICH Q-IWG members for the purposes of a training workshop.

Introduction

- Structure of this session
  - Key Steps in developing a Design Space
  - Presentation of key messages on Design Space
  - Discussion in one or more sub groups on the key questions
  - Wrap up
  - Breakout report

Key Steps for a product under Quality by Design (QbD)



Key Messages (1)

- There are **no regulatory requirements** to have a Design Space
- **Quality Risk Management** approaches need to be considered to ensure the **robustness** of the Design Space
- Design space can illustrate **understanding of parameter interactions** and **provides manufacturing flexibility**
  - Proven acceptable range **alone is not** a design space
- Design space can **include critical and non-critical** parameters
- Design space should be **verified and opperational** at full scale
  - No requirement to develop a design space at the full manufacturing scale
- **Many options** exist for **how (and where)** to present a design space

Key Messages (2) on prior Knowledge

- Prior knowledge may include :
  - Internal knowledge from development and manufacturing
  - External knowledge: scientific and technical publications (including literature and peer-reviewed publications)
- Citation in filing: regulatory filings, internal company report or notebook, literature reference
  - No citation necessary if well known and accepted by scientific community

Key Messages (3) on QRM / DS development

- Risk assessment is based on prior knowledge and relevant experience for the product and manufacturing process
  - **Gaps** in knowledge could be addressed by further experimentation
  - Assignments of risk level must be appropriately justified
- Risk assessments/control will **iterate** as relevant new information becomes available
  - Final **iteration** shows control of risks to an acceptable level

Key Messages (4) – DOE & Modeling

- Target the desired quality attribute range from QTPP
- Determination of edge of failure is not required
- Modeling is not required to develop a Design Space
- Models need to be verified, updated and maintained

Key Messages (5)– Process parameter & quality attributes

- **Design space presentation in the submission could include critical and non-critical parameters**
  - Critical parameter ranges/model are considered a regulatory commitment and non-critical parameter ranges support the review of the filing
  - Critical parameter changes within design space are handled by the Quality System and changes outside the design space need appropriate regulatory notification
- **Non-critical parameters would be managed by Quality System**

Key Messages (6) - Presentation of Design Space in regulatory submission

- **Design Space need to be clearly presented and justified in regulatory submission**
  - Design Space need to be described in sufficient details in regulatory filing
    - Description could include critical and non critical parameters to assure complete understanding
  - Designation of criticality need to be justified in regulatory submission based on QRM and/or experimental results

Training Topics review in Sub Group

- Design Space development
  - Scope and applicability of DS
  - Steps in Development of DS: illustration
  - Prior knowledge
  - QRM
  - DOE & modeling
  - Process Parameter and Quality Attribute as factors in Design Space development
- Implementation of Design Space
- Presentation of Design Space in regulatory submission

Now Break out in sub group

Training Questions

Scope & Applicability of Design Space DS

- Can a DS be applicable to scale-up ?
- Can a DS space be applicable to a site change ?
- Can a DS be developed for single and/or multiple unit operations ?
- Is it possible to develop a DS for existing products ?
- Is there a regulatory expectation to develop a DS for an existing product ?
- Can a DS be applicable to formulation ?

Training Questions

DS development – Key Steps

- What are the key steps developing a DS ?

Steps in Development of Design Space

- Consider QTPP in establishing the Design Space (Back up slide1)
- Initial determination of CQAs
- Assess prior knowledge to understand variables and their impact
  - Scientific principles & historical experience
- Perform initial risk assessment of manufacturing process relative to CQAs to identify the high risk manufacturing steps (->CPPs)
- Conduct Design of Experiments (DoE)
- Evaluate experimental data
- Conduct additional experiments/analyses as needed

QTPP :Quality Target Product Profile

defines the objectives for development

Dosage form and strength	Immediate release tablet taken orally 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

- 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. (ICH Q8 (R2))

Training Questions

DS development - Prior knowledge

- What might be applicable sources of Prior Knowledge ?

DS development - Prior knowledge

Example from Case Study : Crystallization of the drug substance

- Particle size control needed during crystallization
- Prior knowledge/1st principles shows that other unit operations (Coupling reaction, aqueous workup, filtration and drying) have low risk of affecting purity or PSD.
  - Knowledge from prior filings
  - Knowledge from lab / piloting data, including data from other compounds using similar "platform" technologies
  - First principles knowledge from texts/papers/other respected sources

Back up Slide 2 & 3

Training Questions

DS development - QRM

- If the risk acceptance criteria (conclusions) are different than scientific theory/prior knowledge would indicate, then is further explanation provided to justify unexpected conclusions?
- If there are gaps in the information then what would the plan be to make adjustments to further reduce risk?

Workshop A: Design Space

Illustration from the Case Study - Risk Assessment for PSD Control

What is the **Impact** that ---------- will have on purity? 1) minimal 5) moderate 9) significant

What is the **Probability** that variations in ---------- will occur? 1) unlikely 5) moderately likely 9) highly likely

What is our **Ability to Detect** a meaningful variation in ---------- at a meaningful control point? 1) certain 5) moderate 9) unlikely

Unit Operation	Parameter	IMPACT	PROB.	Detect	RPN	Comments
Crystallization	Feed Temperature	1	5	1	5	
Crystallization	Water content of Feed	1	5	5	25	
Crystallization	Addition Time (Feed Rate)	9	5	9	405	Change in addition time is easy to detect, but rated high since there is no possible corrective action
Crystallization	Seed wt percentage	9	5	5	225	
Crystallization	Antisolvent percentage	1	1	1	1	Yield loss to crystallization already low (< 5%), so reasonable variations in antisolvent percentage (+/- 10%) will not affect the percent of batch crystallized, and will not affect PSD
Crystallization	Temperature	9	5	9	405	Change in crystallization temperature is easily detected, but rated high since no possible corrective action (such as, if seed has been dissolved)
Crystallization	Agitation (tip speed)	9	5	5	225	Prior knowledge indicates that final PSD highly sensitive to Agitation, thus requiring further study.
Crystallization	Seed particle size distribution	9	1	1	9	Seed PSD controlled by release assay performed after pin milling.
Crystallization	Feed Concentration	1	1	1	1	Same logic as for antisolvent percentage

To be investigated in DOE

Training Questions

DS development – QTPP and CQAs

- How are CQAs determine ?

Illustration from case study : 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

API Crystallization: Design Space & Control Strategy

Particle Size	Crystallization	Temperature	20 to 30°C	Control between 23 and 27°C
Particle Size	Crystallization	Feed Time	5 to 15 hours	Control via flow rate settings
Particle Size	Crystallization	Agitation	1.1 to 2.5 m/s	Quality system should ensure changes in agitator size result in change to speed setting
Particle Size	Crystallization	Seed Wt%	1 to 2 wt%	Controlled through weigh scales and overcheck
Hydrolysis Degradate	Distillation / Crystallization	Water Content	< 1 wt%	Control via in process assay (e.g. < 0.5%)

Training Questions

Implementation of Design Space

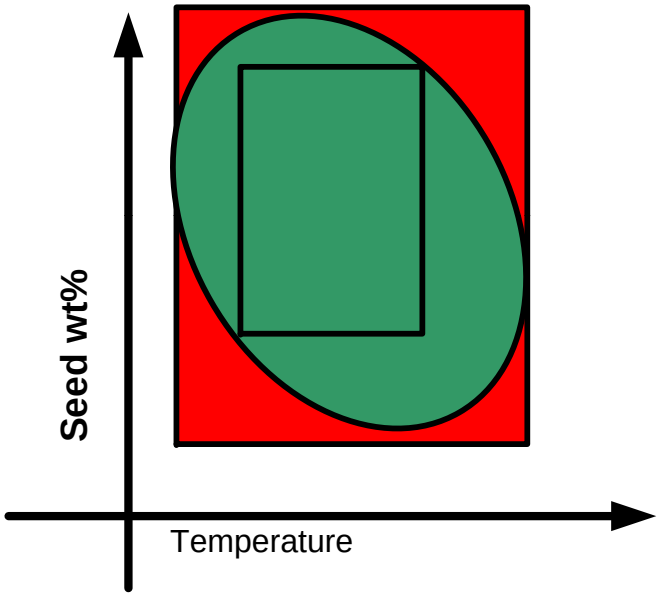
- **What PQS element need to be considered ?**
  - How DS is captured in batch documentation and batch release ?
  - How DS knowledge used in managing changes in the manufacturing process?
- **What information would be transmitted to the manufacturing site?**

Training Questions

Presentation of design space in regulatory submission

- What is needed in the manufacturing process description in the filing to demonstrate the implementation of the Design Space?
- What is the appropriate level of detail to present DOE and it's conclusions in regulatory submissions ?

Illustration from the case study : Options for Depicting a Design Space



- In the idealized example at left, the oval represents the full design space. It would need to be represented by an equation.
- Alternatively, the design space can be represented as the green rectangle by using ranges
  - a portion of the design space is not utilized, but the benefit is in the simplicity of the representation

Large square shows the ranges tested in the DOE
Red area shows points of failure
Green area shows points of success.