Implementation of ICH Q8, Q9, Q10

Design Space

Structure of this session

- Introduction
- DS training objectives
  - 10 min
- Key messages and training topics (in sub groups)
  - 80 min
- Discussion, feedback (in full group, if possible)
  - 15 min
- Breakout report (in full group, if possible)
  - Clarity of the key message
  - Concern
  - Need for clarification
  - 15 min

Introduction

- 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

Training Objectives

- Design Space development
  - Steps in Development of Design Space
  - 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

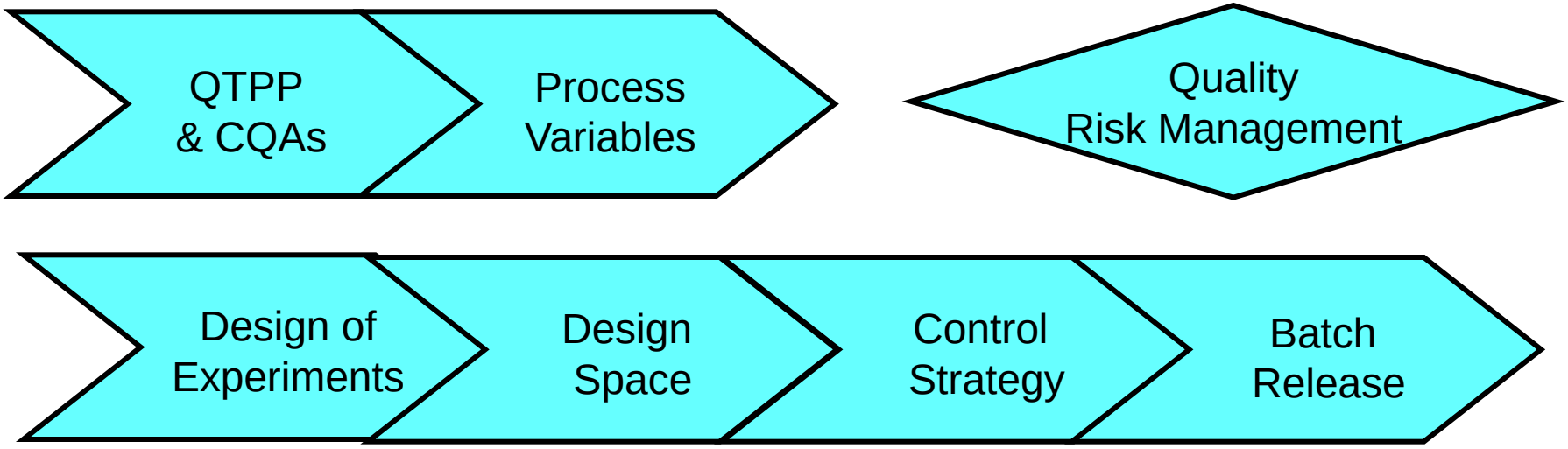
Break out A: Design Space

Now Break out in sub group

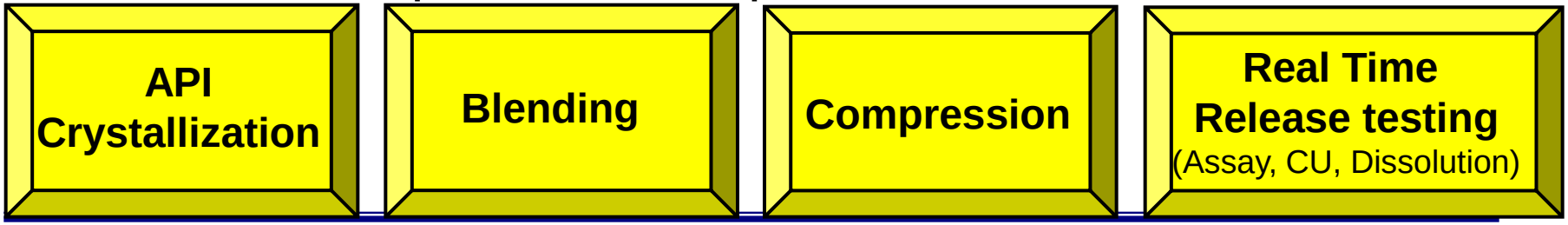
Steps in Development of Design Space

- Consider QTPP in establishing the Design Space
- 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

QbD Story per Unit Operation



Illustrative Examples of Unit Operations:



DS development - Prior knowledge

- Key messages
  - 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

DS development - Prior knowledge

- What might be applicable sources of Prior Knowledge ?
- Identify other type of prior knowledge that can be used in DS development

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

DS development - QRM

- 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

DS development - QRM

- Training questions
  - 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?

Case Study Example

Break out 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

Detailed working documents like this would likely not be included in the submission

DS development – 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

DS development – DOE & Modeling

- Does the DOE results, as presented in the case study, provide sufficient information to define a design space?
- Describe which parameters are addressed by univariate vs. multivariate DOEs and how these are factored into the design space
- Model implementation: Describe how variability due to the process operations and/or analytical method is considered in use of the model
- Describe the process for maintenance & updating of the model

DS development – 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**

DS development – Process parameter & quality attributes

- Illustration & training questions
  - Has the model for PSD Control (next slide) been demonstrated to be scale and equipment independent?
  - Is a mathematical model always needed to have a design space?
  - How to evaluate the impact of changing non-critical process parameters when included in the design space ?
    - Technical evaluation of a change of non-critical is the same scientific principle as for critical

Break out A: Design Space

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.

Drug Product CQAs

- •Assay
- •Content Uniformity
- •Dissolution
- •Tablet Mechanical Strength

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

CQAs may be ranked using quality risk assessment.

Break out A: Design Space

API Crystallization: Design Space & Control Strategy

Particle Size	Crystallization	Temperature	20 to 30ºC	Control between 23 and 27ºC
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%)

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?**

Presentation of Design Space in regulatory submission

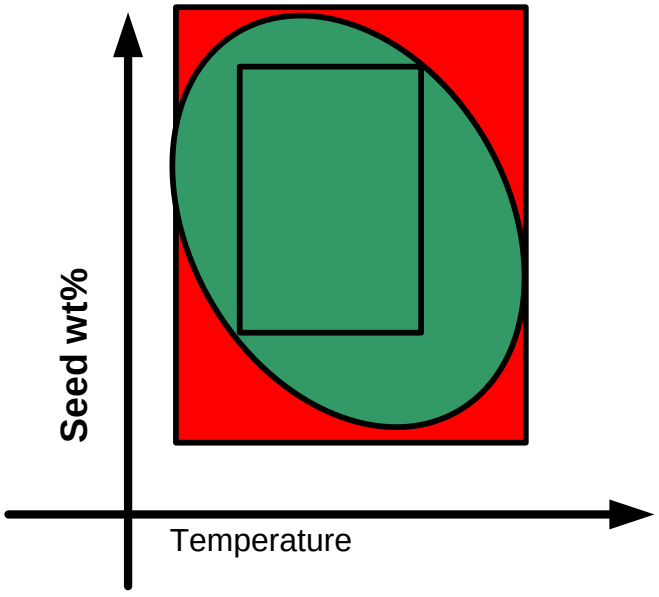
- **Design Space need to be clearly presented and justified in regulatory submission**
  - Design Space need to be described in sufficient details in regulatory filing
    - Description could include critical and non critical parameters to assure complete understanding
  - Designation of criticality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

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 ?

Break out A: Design Space

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.