Design Space Considerations

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Outline

- Definition of design space
- Role of statistics in design space
- Defining a design space
- Communicating design space in regulatory filings
- Implementing and maintaining a design space
- Conclusion

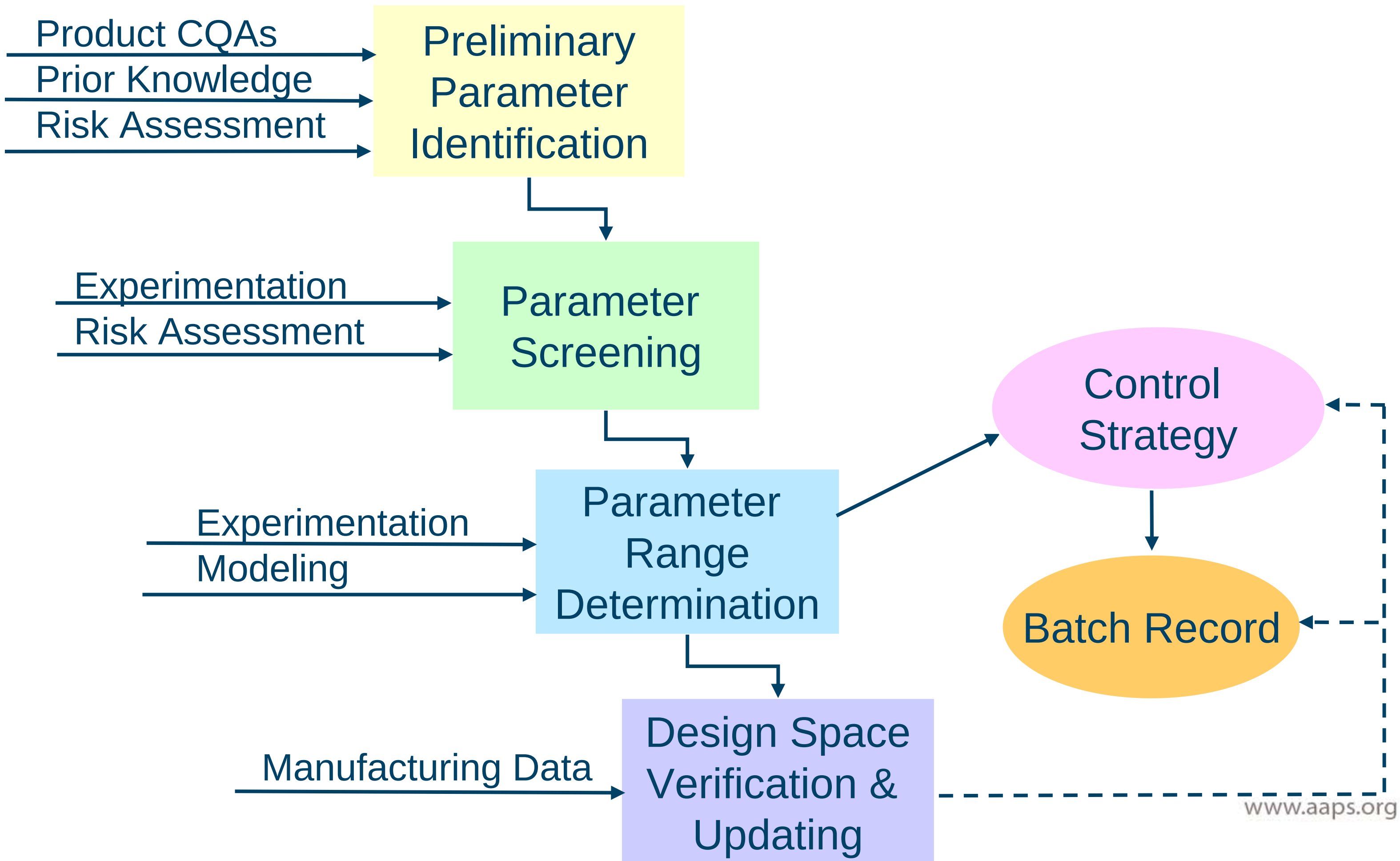
What is Design Space?

- Scientific concept for ensuring quality
  – Multidimensional parametric space within which acceptable quality product is obtained
    - Includes input material attribute and process parameter ranges
  – Is proposed by the applicant
- Regulatory concept
  – Defines allowable operational flexibility
  – Specific to a product and process

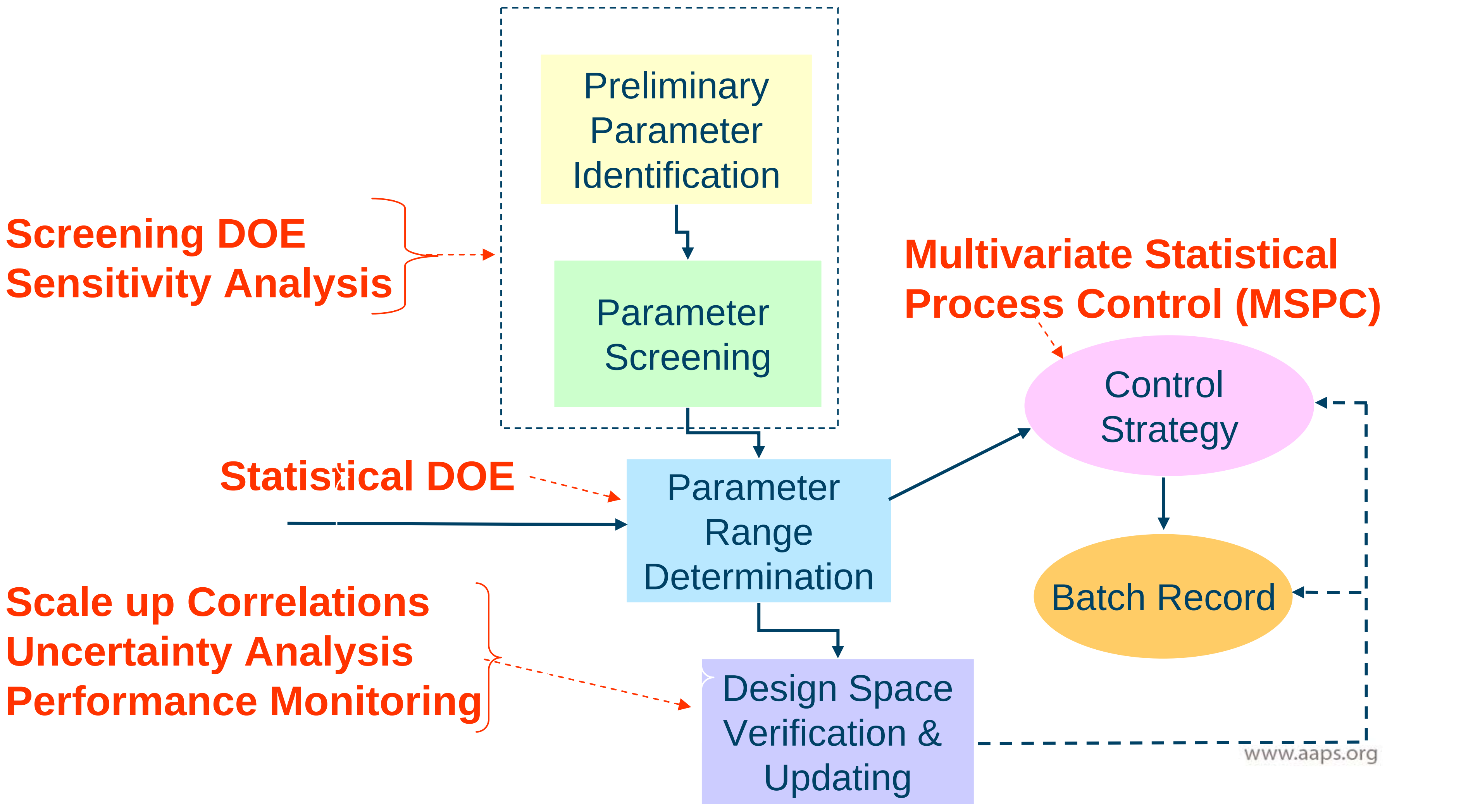
Design Space Definition (ICH Q8R2)

- Definition
  - The multidimensional **combination and interaction of input variables** (e.g., material attributes) and process parameters that have been **demonstrated to provide assurance of quality**.
- Regulatory flexibility
  - Working within the design space is not considered as a change
- Important to note
  - Design space is proposed by the applicant and is subject to regulatory assessment and approval

Example Approach for Defining a Design Space



Example of Statistical Tools



Considerations for Defining a Design Space

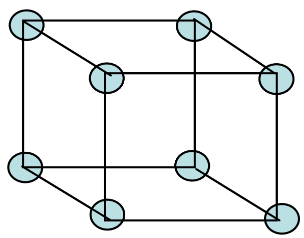
- Include material attributes and process parameters that affect product CQAs
  - Risk Assessment is a valuable tool to identify parameters
  - Allows ranking of parameters
- Scale-independent parameters, if design space is applicable to multiple scales
- Design space can be developed for one unit operation or for entire process
  - Evaluation of impact of interaction of design spaces

Examples of Defining Design Space from Regulatory Filings

Regression Model based Design Space: Empirical Approach

1. Choose experimental design

(e.g., full factorial, d-optimal)

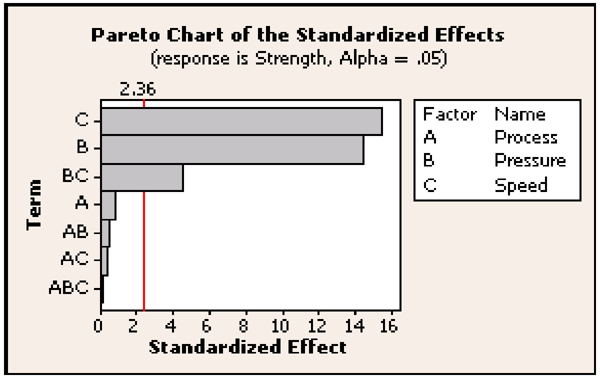


2. Conduct randomized experiments

Experiment	Factor A	Factor B	Factor C
1	-	-	-
2	+	+	-
3	-	+	+
4	+	-	+

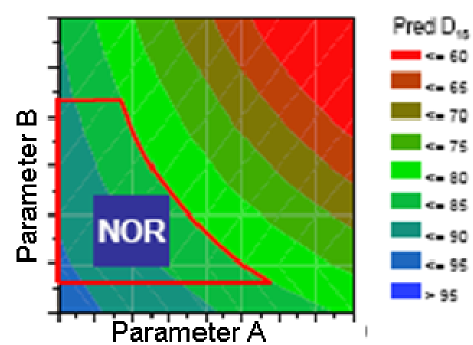
3. Analyze Data

Determine significant factors



4. Define Design Space

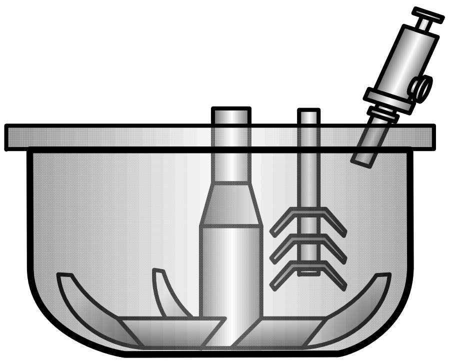
As a contour surface and/or regression model



Prediction algorithm:

$Diss = 108.9 - 11.96 \times API - 7.556 \times 10^{-5} \times MgSt - 0.1849 \times LubT - 3.783 \times 10^{-2} \times Hard - 2.557 \times 10^{-5} \times MgSt \times LubT$

Scale Independent Design Space: Hybrid Approach



High Shear Granulator (HSG)

Process parameters for high shear granulation represented by a dimensionless number:

> **Spray Flux:** Measure of area wetted by drops from spray nozzle to powder flux through spray zone

↓

Multivariate DOE to study granulation at pilot scale:

> **Inputs:** amount of granulation liquid, impeller speed, granulation time

↓

Analysis of DOE data used to define a **scale invariant** design space in terms of range of **Spray Flux**

Uncertainty in Design Space

- Design spaces have inherent uncertainty
  - Variability in experimental measurement
  - Model estimations
  - Limited ranges studied
  - Validity of underlying assumptions (e.g., unknown variables, parameters held constant)
  - Effect of different scales or equipment
- Statistical treatments (e.g., Monte Carlo simulations, Bayesian approach) can help evaluate the effects of uncertainty
- Risks from uncertainty can be addressed in implementation of design space
  - Performance Monitoring
  - Risk-based change control performed under firm's quality system

Example of Uncertainty Analysis (I)

Design Space defined on the basis Multivariate Design Of Experiments (DOE) results

DOE Ranges:
API: 0.5 - 1.5
MgSt: 3000 – 12000
LubT: 1 – 10
Hard: 60 – 110

API:	Particle size of the active, log(d(0.9)), μm
MgSt:	Magnesium Stearate specific surface area, cm^2/g
Lub T:	Lubrication time, min
Hard:	Tablet hardness, N

Adapted from ICH IWG Training, October, 2010

Example of Uncertainty Analysis (II)

Regression model from DOE data

CQA

Prediction algorithm:

$$\text{Diss} = 108.9 - 11.96 \times \text{API} - 7.556\times10^{-5} \times \text{MgSt} - 0.1849 \times \text{LubT} - 3.783\times10^{-2} \times \text{Hard} - 2.557\times10^{-5} \times \text{MgSt} \times \text{LubT}$$

Diss: % dissolved in 20 minutes,

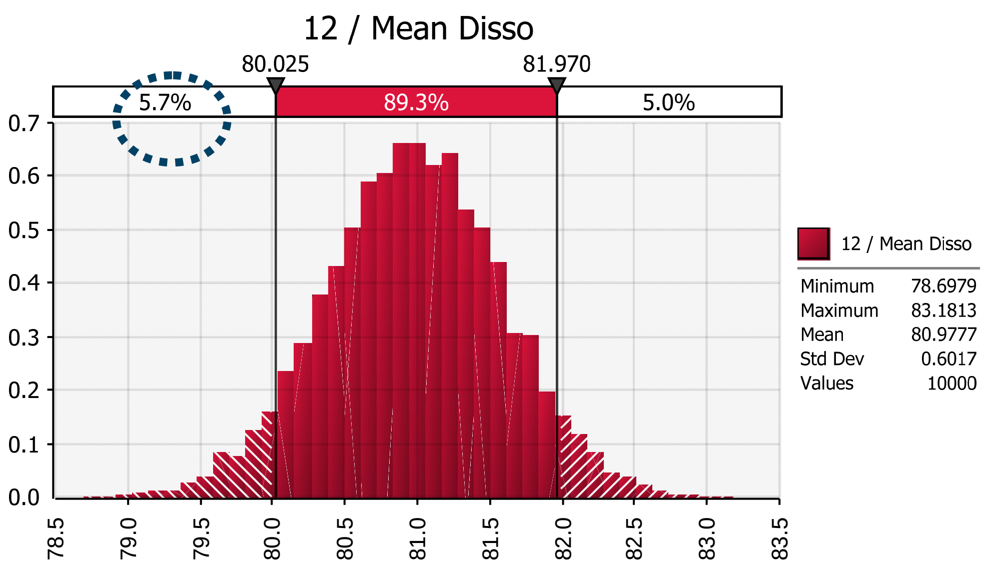
Specification: 80% dissolved in 20 min

Adapted from ICH IWG Training, October, 2010

Results from Monte Carlo Simulation

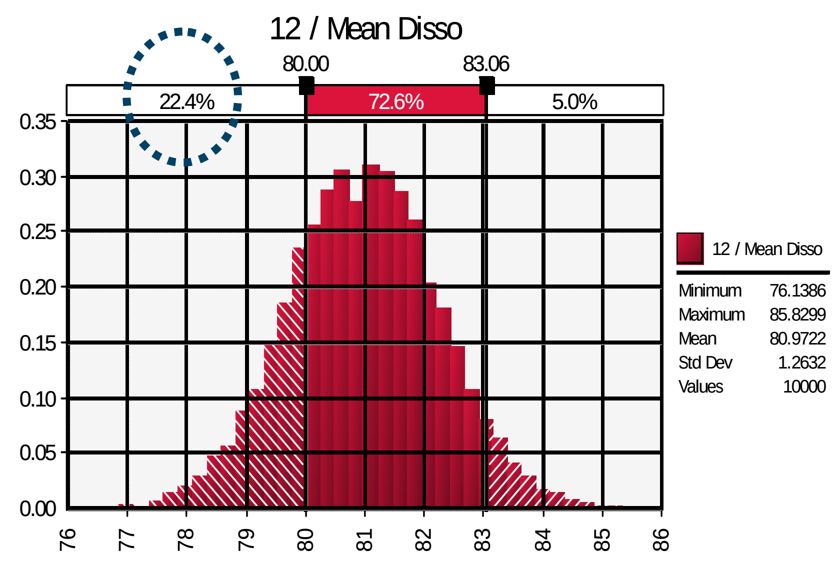
Estimation of potential for dissolution failure at one of the edges of design space (API: 1.5, MgSt: 12000, LubT: 10, Hard: 110)

Considering Measurement Uncertainty



There is a ~94% 'assurance of quality'

Considering Measurement and Model Coefficient Uncertainty



There is a ~78% 'assurance of quality'

Ref: Adapted from 'Evaluation of Process Models with Monte Carlo Methods' Kauffman, J., Chatterjee, S. Geoffroy, J-M, IFPAC Annual Meeting, 2012

Some Common Misconceptions about Design Space Development

- Design of Experiments (DoE) is the same as Design Space
  - DoE is not the only method for determining a design space
- Only critical parameters should be in a design space
  - Can include all parameters affecting product quality
  - Can include parameters that were held constant
- Edge-of-failure is needed for a design space
  - Failure mode experiments provide useful information, but not required

Submitting a Design Space

What Information Should be in the Application to Support a Design Space?

- Process parameters and material attributes
  - those that were included in the design space
  - those were not varied should be discussed as appropriate to fully describe the manufacturing process
- Rationale for inclusion in the design space
- Effect of the process parameters and material attributes on product CQAs
- Include more detail (e.g., raw data and statistical analysis) for medium impact models e.g. design space defined in terms of a model

How Can a Design Space be Described?

- Presentation of design space can include
  - Linear Ranges of Parameters
  - Mathematical Relationships
  - Time-dependent functions
  - Combinations of variables (e.g., principle components of multivariate model)
- Scope of design space can include
  - Multiple scales, (e.g., scaling factors)
  - Single or multiple unit operations

The applicant decides how to describe and present the design space

Examples of Communication of Design Spaces

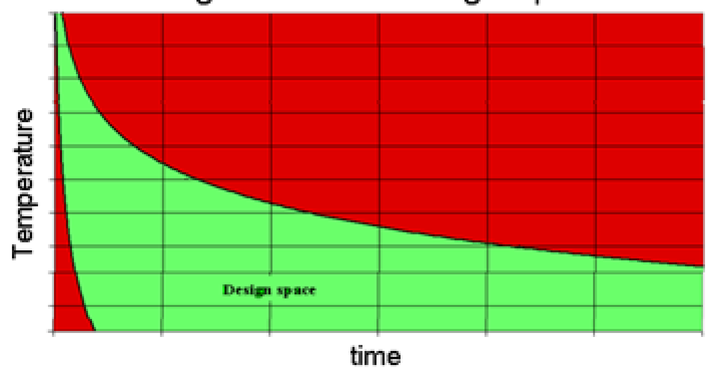
Example 1: Linear Ranges

Design Space for Film Coating

Parameter	Design Space
Pan Load Size	xx - xx kg
Final Spray Rate Set Point	xx – xx mL/min
Inlet Temperature Set Point	xx – xx ° C
Outlet Temperature Set Point	xx – xx ° C
Air Flow to Spray Rate Ratio Set Point	xx – xx (m3/hr)/ (mL/min)
Final Drum Speed Set Point	xx –xx rpm
Target Core Tablet Weight Gain	Minimum x% prior to drying/cooldown
Cool Down Temperature	≤ xx ° C

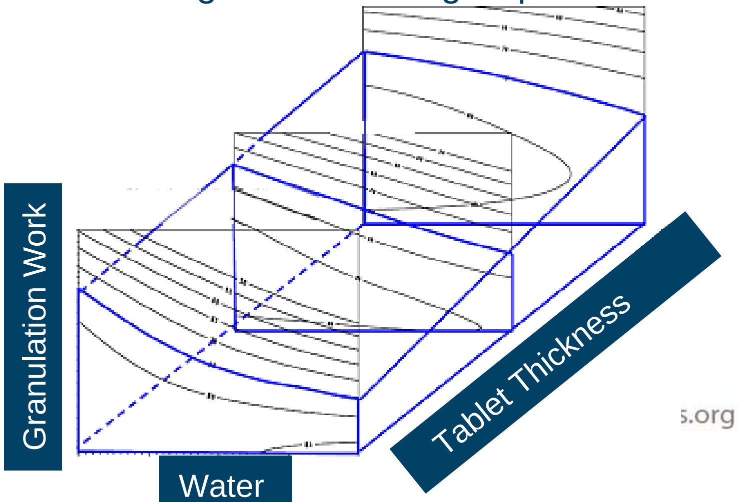
Example 2: 2-D Graphical

Drug Substance Design Space



Example 3: 3-D Graphical

Drug Product Design Space



Some Common Misconceptions about Design Space in Applications

- Design space need to be expressed as linear ranges
- Proven Acceptable Ranges (PAR) means the same as Design Space
- A design space can be defined by process outputs
  - Inconsistent with design space definition in ICH Q8(R2)
- If the product is manufactured within the design space, no specifications or end-product testing is needed
  - Specifications are required by regulations
    (CFR § 314.50(d) and CFR § 211.165(a))

Proven Acceptable Ranges

- Multiple interpretations exist for Proven Acceptable Ranges (PARs)
  - Parameters studied univariately, without consideration of interactions (ICH Q8 definition)
  - Parameters studied multivariately but no interactions found
  - Linear parameter ranges (studied either with or without consideration of interactions)
- Use of the term “PAR” should be clearly defined within application and how it is intended to be used

Process Outputs

- Process outputs do not define a design space
- Even when controlling process outputs, the design space of input parameters can be important
  - Many process results are path dependent
  - Effects on multiple parameters need to be considered (not just measured parameter)
  - Response of a system is usually only known over demonstrated range

Maintaining a Design Space

Design Space Verification and Maintenance

Additional monitoring and sampling, under the quality system, could be merited to verify and/or maintain the design space:

- When a design spaces constructed at laboratory and pilot scale is translated to commercial scale
- For movement within a design space to commercially unverified area
- On a periodic basis, as a part of process maintenance

Considerations for Design Space: Verification and Maintenance

- Commercial scale verification of design space
  - Dependent on methodology for scaling up design space
    - Scale dependent or independent
    - Inherent scale up risks
  - Bracketing approach may be used
  - Can include appropriate risk mitigation steps
    - Example: Enhanced sampling or monitoring for movements to commercially unverified areas of design space
  - May be an element of Continuous Process Verification
- Maintenance
  - Quantitative comparisons more useful than PASS/FAIL
  - Triggers may be changes in incoming materials or equipments

Reporting Changes to Design Space

- Movement within design space does not need reporting
- Contraction of design space typically in Annual Report
- Expansion of design space require regulatory notification and potential prior approval
  - In concurrence with 21 CFR 314.70

Some Common Misconceptions about Design Space Implementation

- Certain movements within a design space require regulatory notification
  - Inconsistent with ICH Q8(R2)
- No change control is needed with an approved design space
  - Although no regulatory notification is needed, movement within a design space needs to be managed under the firm's quality system
  - Appropriate verification of new process set points should be performed

Concluding Comments

- Considerations for design space
  - Use a risk-based and multivariate approach
  - Understand uncertainty in design space
  - Support implementation through quality systems
  - Clearly communicate the intended design space to regulators
- FDA welcomes discussion on design space with applicants
  - Recommended approach is discussions at EOPII meetings, or earlier

Thank you!

Questions, comments, concerns:

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