Pharmaceutical Development: ICH Q8/Q(8)R

Moheb M. Nasr, Ph.D..

Office of New Drug Quality Assessment
Center for Drug Evaluation and Research (CDER)
Food and Drug Administration (FDA)

Workshop on Implementation of ICH Q8/Q9/Q10
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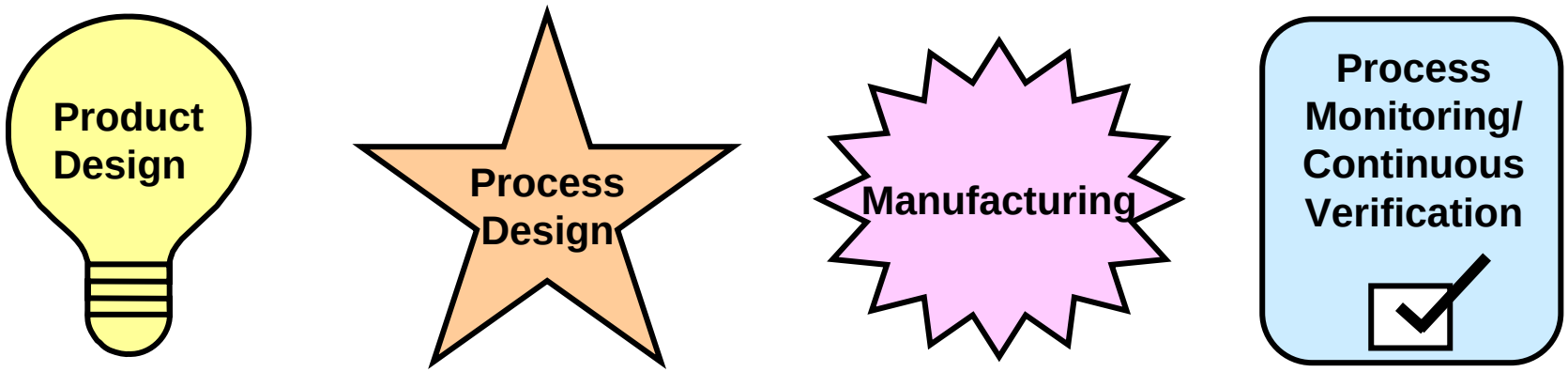
Outline

- Recent ICH and FDA Guidances
- ICH Q8 and Q8(R)
- Quality by Design (QbD)
  - Example Approach to QbD
  - QbD for APIs
- FDA Experience with QbD
  - ONDQA QbD Pilot Program
- Challenges of Implementing QbD
- Concluding Remarks

Recent ICH & FDA Guidances



ICH Q8/Q8(R) - Pharmaceutical Development

FDA PAT Guidance

ICH Q9 – Quality Risk Management

ICH Q10 – Pharmaceutical Quality Systems

ICH Q8 Guidance

- Provides guidance on the contents of Section 3.2.P.2 (Pharmaceutical Development)
- Describes good practices for pharmaceutical product development
- Introduces concepts of
  - Design space
  - Flexible regulatory approaches
  - Quality Risk Management (Q9)
- Does not discuss QbD

QbD Definition (ICH Q8(R))

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

Why QbD?

- Higher level of assurance of product quality
- Cost saving and efficiency for industry
  - Increase efficiency of manufacturing process
  - Minimize/eliminate potential compliance actions
  - Provide opportunities for continual improvement
  - Facilitate innovation
- More efficient regulatory oversight
  - Enhance opportunities for first cycle approval
  - Streamline post approval manufacturing changes and regulatory processes
  - More focused PAI and post approval cGMP inspections

ICH Q8R

- Annex to ICH Q8
- Describes principles of QbD vs. minimal approach
- Provides further clarification of key concepts of Q8
- Provides illustrative examples
- ***Details provided in the next Presentation -Brian Withers, Abbott Laboratories***

ICH Q8(R) Update

- Reached Step 4 in Brussels, November 11, 2008
- Only a few minor step 4 revisions:
  - Quality Target product Profile
    - QTPP forms the basis of design for development
  - Design space versus proven acceptable ranges
    - combination of PARs doesn't constitute design space
  - Real Time Release Testing (RTRT)
    - To distinguish between RTRT and batch release

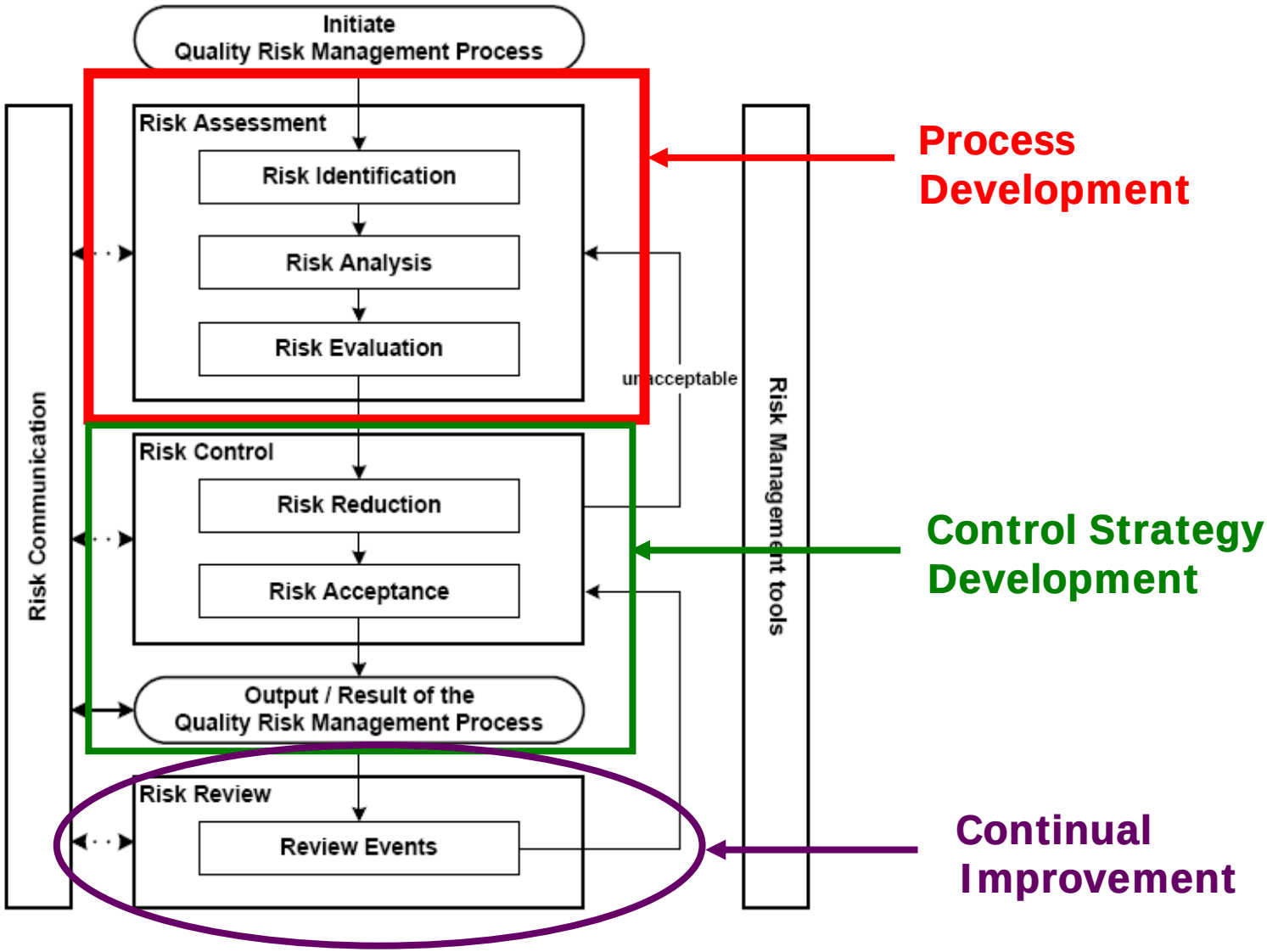
ICH Q9 and Q10

- Key enablers
- Assure correct implementation of QbD (Development & manufacturing throughout product life cycle and supply chain)
- Both will be discussed in more details tomorrow

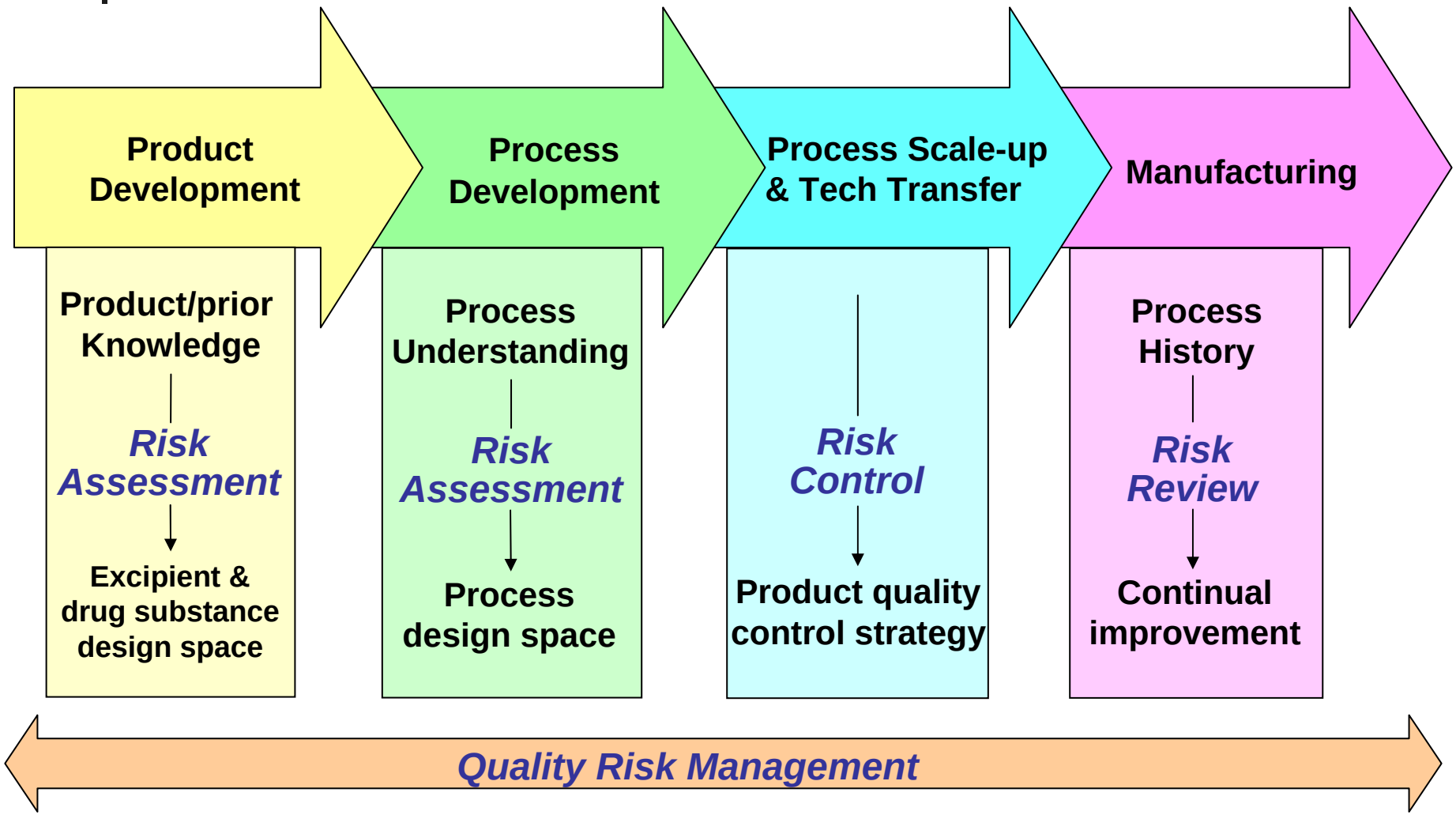
ICH Q9: Quality Risk Management

- A systematic process for the assessment, control, communication and review of risks to the quality of the drug product
- Guidance includes principles and examples of tools for quality risk management
- Evaluation of risk to quality should:
  - be based on scientific knowledge
  - link to the protection of the patient
- Applies over product lifecycle: development, manufacturing and distribution

Quality Risk Management Process



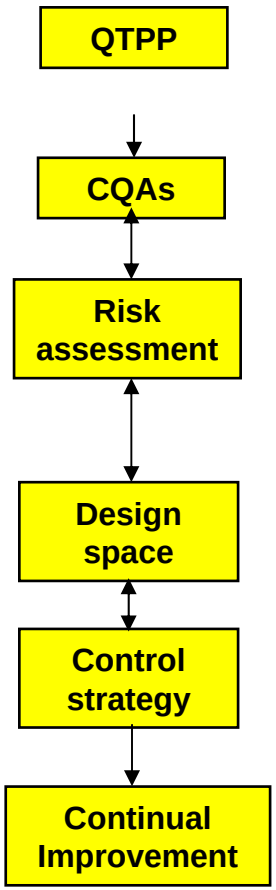
Role of Quality Risk Management in Development & Manufacturing



ICH Q 10: Why Focus on PQS?

- The regulatory flexibility provided with a design space approach requires effective change management at the manufacturing site
  - Track and trend product quality
  - Respond to process trends before they become problems
  - Maintain and update models as needed
  - Internally verify that process changes are successful

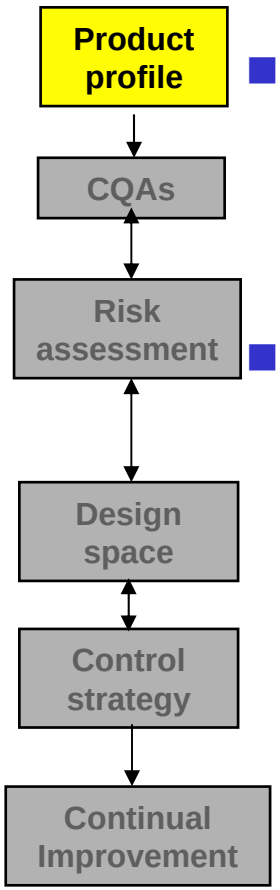
Example QbD Approach (ICH Q8R)



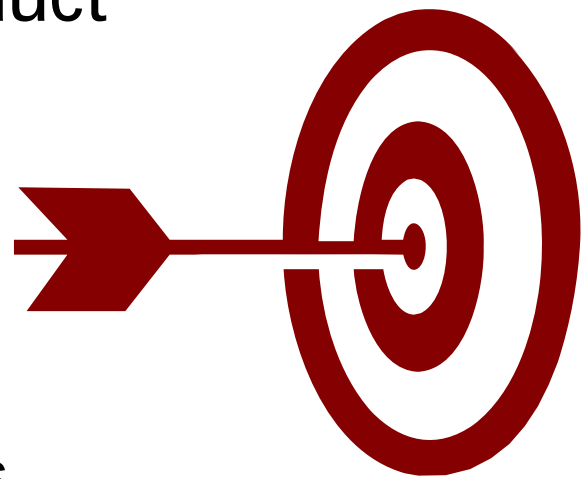
- Target the product profile
- Determine critical quality attributes (CQAs)
- Link raw material attributes and process parameters to CQAs and perform risk assessment
- Develop a design space
- Design and implement a control strategy
- Manage product lifecycle, including continual improvement

Quality Target Product Profile

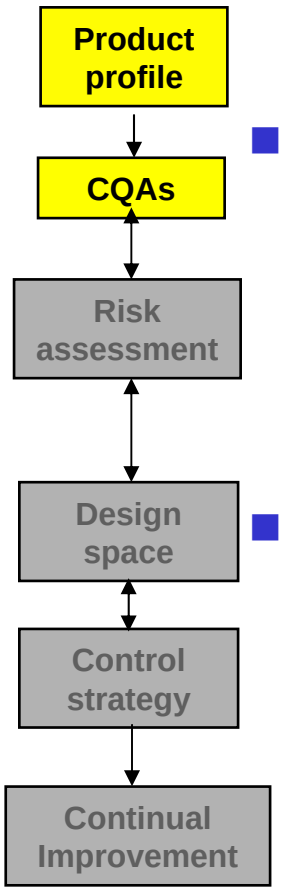
"Begin with the end in mind"



- Summary of the quality characteristics of a drug product to ensure safety and efficacy
- Includes, but not limited to:
  - Dosage form
  - Route of administration
  - Pharmacokinetic characteristics
    - e.g., dissolution, aerodynamic performance
  - Quality characteristics for intended use
    - e.g., sterility, purity

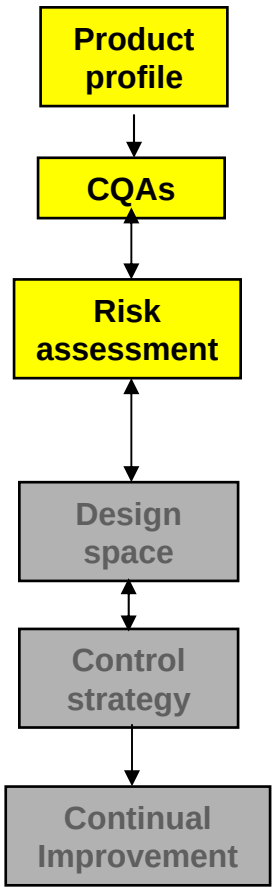


Critical Quality Attributes (CQAs)



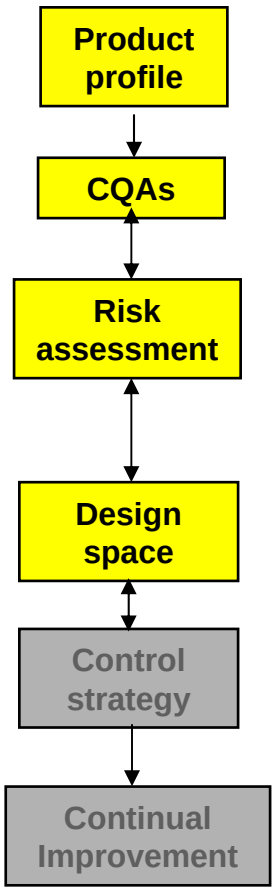
- Physical, chemical, biological or microbiological property or characteristic
- Drug product, drug substance, intermediates, and excipients can possess CQAs
  - Directly affect product quality
  - Affect downstream processability
- Drug product CQAs affect product quality, safety, and/or efficacy
  - Attributes describing product purity, potency, stability and release
  - Additional product specific aspects (e.g., adhesive force for transdermal patches)

Risk Assessment (ICH Q9)



- Tools for parameter screening
  - Examples: Ishikawa diagrams, What-if analysis, HAZOP analysis
- Tools for risk ranking
  - Examples: FMEA/FMECA, Pareto analysis, Relative ranking
- Experimental tools for process understanding
  - Examples: Statistically designed experiments (DOE), mechanistic models

Design Space (ICH Q8)



- Definition
  - The multidimensional combination and interaction off 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 a change
- Important to note
  - Design space is proposed by the applicant and is subject to regulatory assessment and approval

Design Space Determination

- First-principles approach
  - combination of experimental data and mechanistic knowledge of chemistry, physics, and engineering to model and predict performance
- Non-mechanistic/empirical approach
  - statistically designed experiments (DOEs)
  - linear and multiple-linear regression
- Scale-up correlations
  - translate operating conditions between different scales or pieces of equipment
- Risk Analysis
  - determine significance of effects
- Any combination of the above

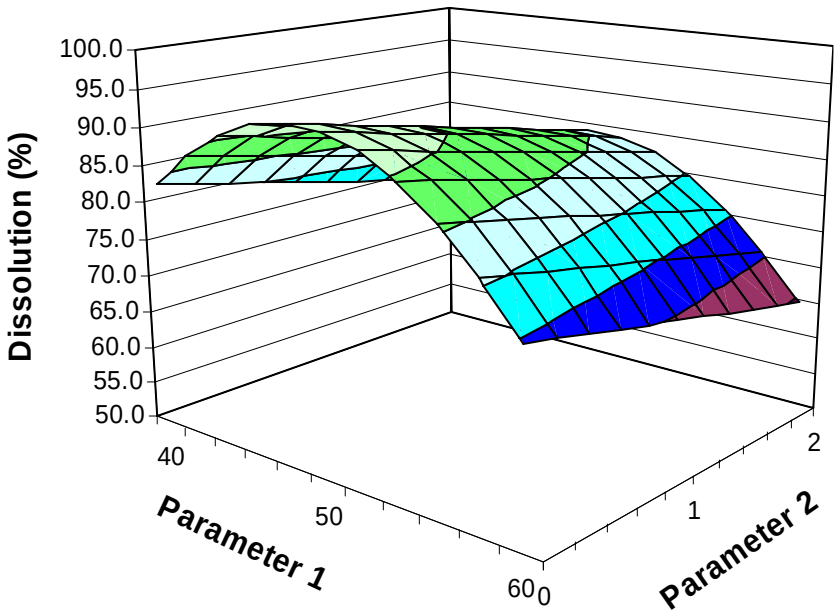
Describing Design Spaces

- Linear Ranges of Parameters
- Mathematical Relationships
- Time-dependent functions
- Combinations of variables
  - e.g., Principle components of multivariate model
- Scaling Factors
- Single or multiple unit operations

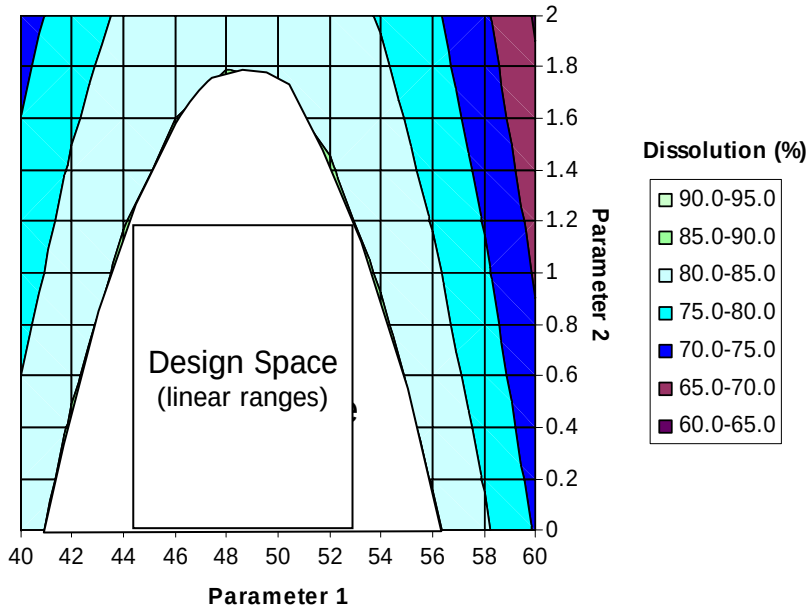
The applicant decides how to describe and present the design space

Design Spaces Example #1

Surface Plot

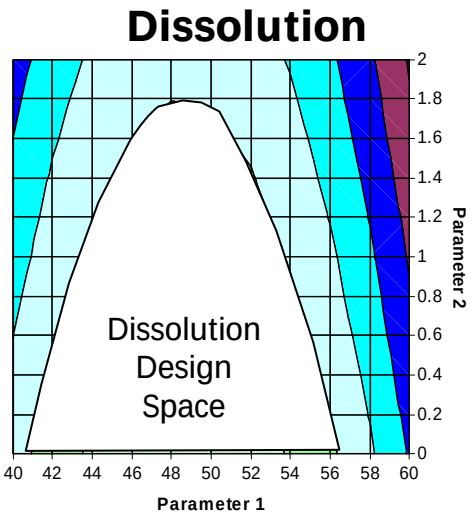


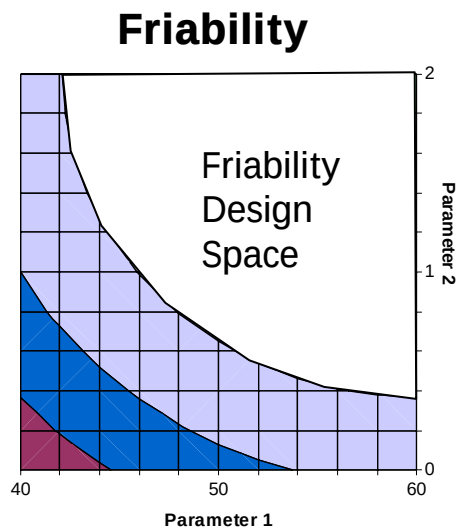
Contour Plot



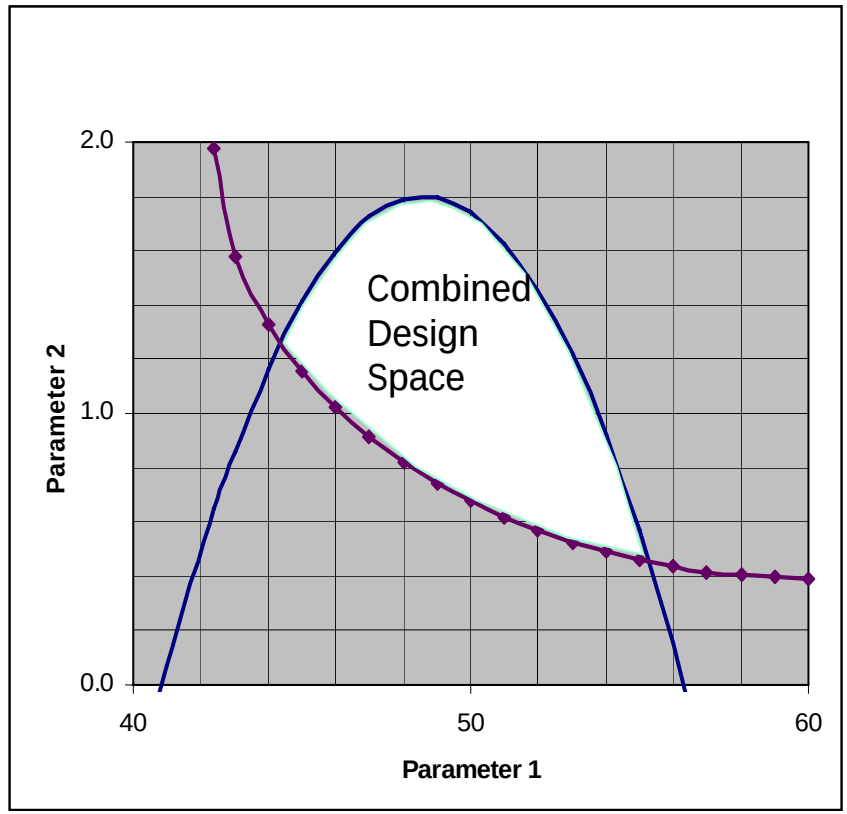
- Design space can be described as a mathematical function or simple parameter range
- Operation within design space will result in a product meeting the defined quality attributes

Design Spaces Example #2

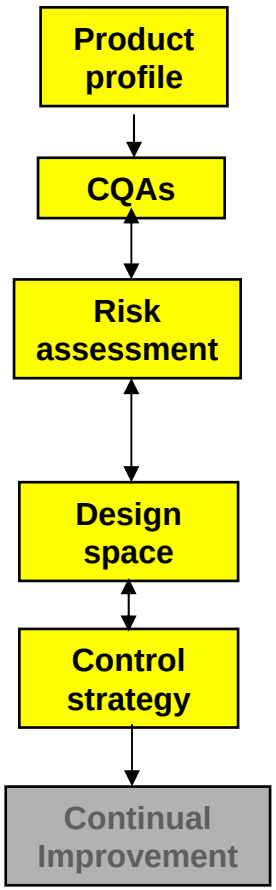


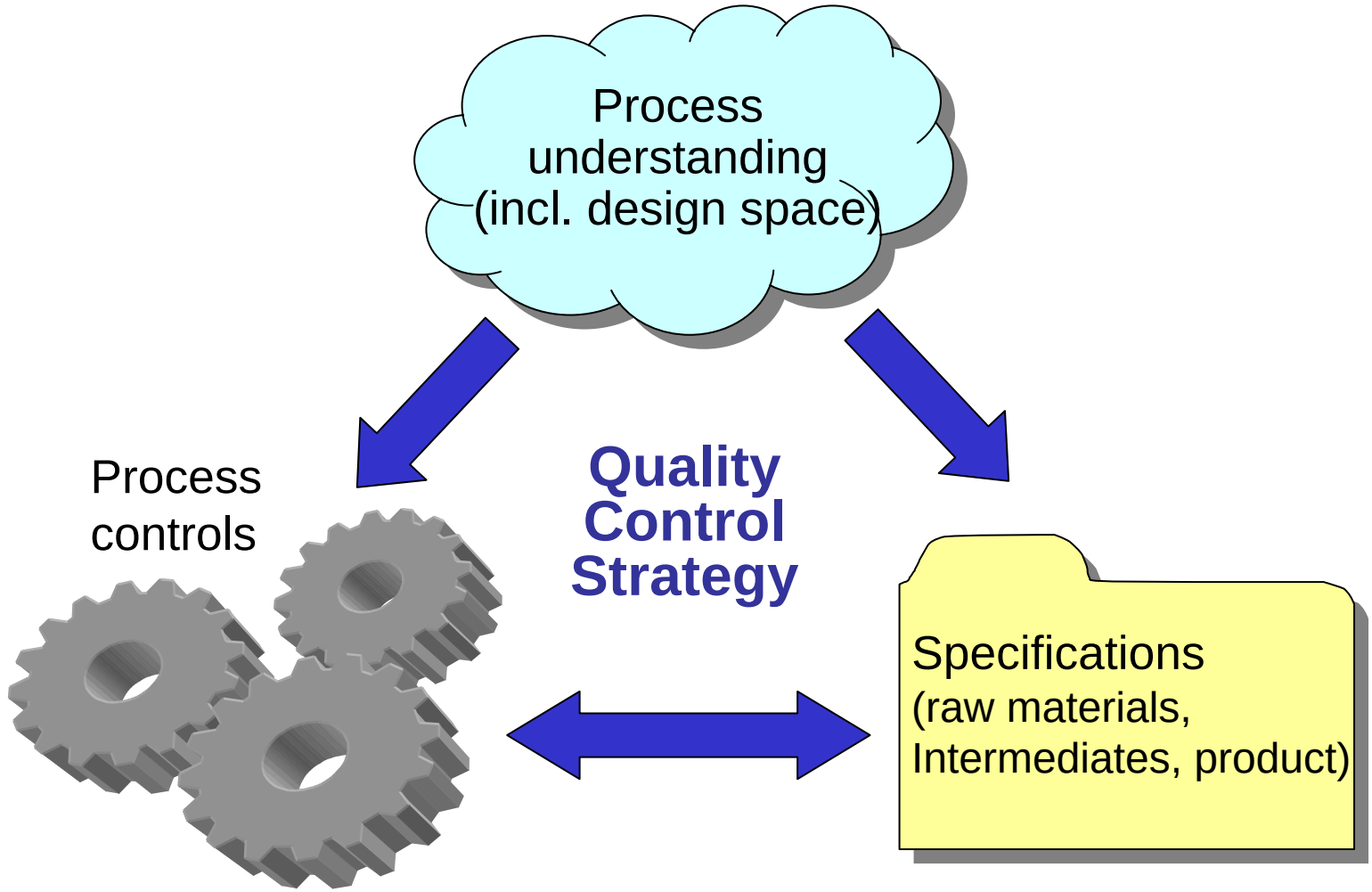


Design space for multiple attributes



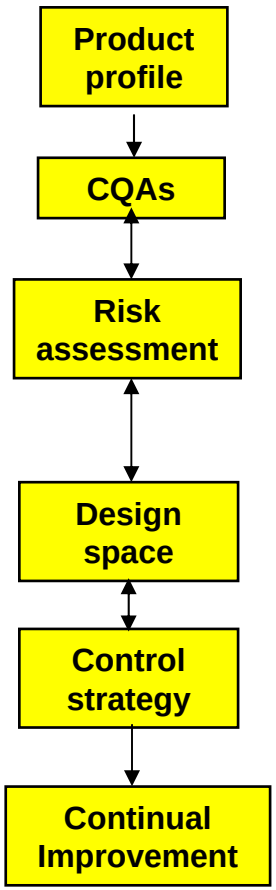
Quality Control Strategy





Quality control strategy encompasses process controls and specifications, based on process understanding

Continual Improvement



- Flexibility for movement within design space
  - Wider range of material attributes or process parameters
  - No reporting if moving operating range within design space
  - Potential scale or equipment change without supplement (subject to regional regulatory requirements)
- Post-Approval Management Plan (CMC-PMP)
  - A mechanism for applicant to propose a regulatory strategy specific to a product and/or process
  - Currently under development by FDA

QbD Concepts in Development and Manufacturing of API

- It may be simpler to apply QbD concepts to drug substances than drug product
- Mixing and transport within liquids and slurries better understood than for dry particles
- Well-established modeling techniques
  - Reaction kinetics
  - Cell growth
  - Crystallization nucleation and growth
  - Scale-up correlations
- Readily available in-line and on-line measurement techniques
- Laboratory equipment for parallel experiments and automated analysis

Example Risk Assessment for Batch API Synthesis Step

Category	Process Parameter	Severity S (1-5)	Occurrence O (1-5)	Detection D (1-5)	Risk priority number S*O*D	Risk Ranking/Prioritization
Crystallization	Residual solvent level	5	4	3	60	1
	Nucleation time	4	3	2	24	6
	Anti-solvent addition rate	5	3	2	30	4
	Agitation rate	4	2	1	8	11
	Seed amount	4	4	2	32	3
	Hold time	2	1	1	2	15
Filtration	Agitation rate	5	2	3	30	4
	Wash step	3	1	1	3	13
Drying	Agitation rate	5	3	3	45	2
	Temperature	4	2	3	24	6

Risk ranking helps focus research and development efforts

ONDQA's QbD Pilot Program

- Objectives
  - To provide participating firms an opportunity to submit CMC information demonstrating QbD
  - To enable FDA to implement new QbD concepts
- Status
  - 9 original and 3 supplemental NDAs accepted
  - 11 submitted to date: 9 approved, 2 under review
  - Common factors
    - Submission of design space
    - Use of risk assessment
    - Proposals of regulatory flexibility under firm's quality system

Examples of Design Space in Recent NDAs

- Excipient attributes
  - Degree of polymer substitution
  - Viscosity/molecular weight distribution
  - Particle size distribution
- Drug substance attributes
  - Particle size distribution
- Process parameters
  - Drug substance unit operations
  - Drug product unit operations
  - Effect of scale-up considered
  - Effect of equipment type understood

CMC Pilot Program – Design Space Observations

- Most applications included a design space for drug product; some for drug substance
- Most included design spaces for process parameters; some included formulation component properties
- Methods for determining design space included:
  - One variable at a time experiments
  - Statistically designed experiments (DOE's)
  - Modeling approaches

CMC Pilot Program – Control Strategy Examples

- Certain tests for drug substance CQAs moved upstream to the control points
- On-line analyzers (non-PAT) used for intermediates
- In-process testing (in lieu of end-product testing) for
  - Identification and assay using at-line NIR
  - Dose uniformity by on-line weight variation
- Real-time release testing

CMC Pilot Program – Risk Assessment Observations

- Several applications presented risk assessments
  - Linking of process parameters to CQAs
  - Identification of relevant parameters for design space
  - Weighting of processing risks and experimental priorities
  - Tools used included Ishikawa (fishbone) diagrams, FMEA analysis, Pareto analysis

Findings from ONDQA Pilot Program

- Provided valuable experience for industry and FDA in implementing QbD
  - Elements of QbD in submissions
    - Risk assessments
    - Design spaces
    - Proposals for flexible regulatory approaches
  - Risk-based regulatory decisions were enabled
- Pointed out gaps
  - Learning from pilot applied to ICH Q8 (R)
  - Demonstrated the need for:
    - Harmonized implementation (ICH IWG)
    - Post-Approval Management Plan (CMC-PMP)

Challenges of Implementing QbD

- FDA
  - Communicating new concepts
  - Providing regulatory flexibility while assuring product quality
  - Integration of review and inspection under the new ICH quality paradigm
- Industry
  - Management support
  - Communication across business units
  - Global acceptance and implementation
- FDA and industry
  - Cultural changes needed
  - More resources needed initially (Investment)
  - Learning and experience needed for new approaches

Concluding Remarks

- Quality by Design has moved into the implementation phase
  - New guidelines are in place to facilitate
  - Recent NDAs (incl. ONDQA pilot program) have provided opportunities for implementing QbD
- Full implementation of QbD is a win-win-win situation
  - Manufacturers – Better understanding of product/process, more efficient process, reduced regulatory burden
  - Regulators – providing regulatory flexibility without sacrificing quality
  - Patients – increased assurance of product quality

Pathway to the Desired State

The Desired State:
A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight.