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ICH Q8/Q8R – Pharmaceutical Development

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Outline

- Background on ICH Q8/Q8R
  - Quality by Design (QbD)
- FDA experience with QbD
  - Examples from CMC Pilot
  - Recent ONDQA experience
- Remaining challenges
- Concluding comments

ICH Q8 - History

- ICH Quality Vision – July 2003 (Brussels)

  Develop a harmonized pharmaceutical quality system applicable across the lifecycle of the product emphasizing an integrated approach to risk management and science
- Q8 Step 2 (draft for comment) – Nov 2004
- Q8 Step 4 (finalized) – Nov 2005
- Q8 Annex Step 2 (draft for comment) – Nov 2007
- Q8(R1) Step 4 (final) – Nov 2008
- Q8(R2) Revision for editorial errors – Aug 2009

ICH Q8 Core Document - Content

- 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 Quality by Design

Key Points from ICH Q8 Core Document

- Quality cannot be tested into products, it should be built in by design
- Pharmaceutical development provides the scientific understanding to support the establishment of design space, specifications and manufacturing controls
- Aspects of pharmaceutical development include:
  - Components of Drug Product
  - Drug Product Development
  - Manufacturing Process Development
  - Container Closure System
  - Microbiological Attributes
  - Compatibility

ICH Q8(R2) - Content

- Defines and describes principles of Quality by Design (QbD)

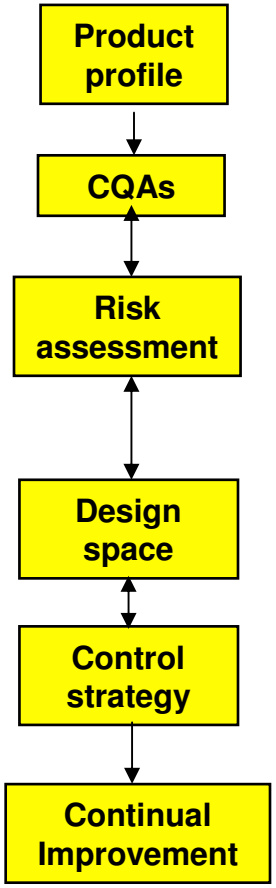
  Quality by Design is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management

- Provides further clarification of key concepts of Q8
- Provides illustrative examples

Key Points from ICH Q8 Annex Document

- Minimal Approach
  - Defining the quality target product profile
  - Identify potentially critical quality attributes of drug product
  - Determine critical quality attributes of the drug substance and raw materials
  - Selecting an appropriate manufacturing process
  - Defining a control strategy
- Enhanced (QbD) Approach
  - Systematic evaluation and understanding of the formulation and manufacturing process
  - Using the enhanced understanding with risk management to establish an appropriate control strategy
  - Can support flexible regulatory approaches

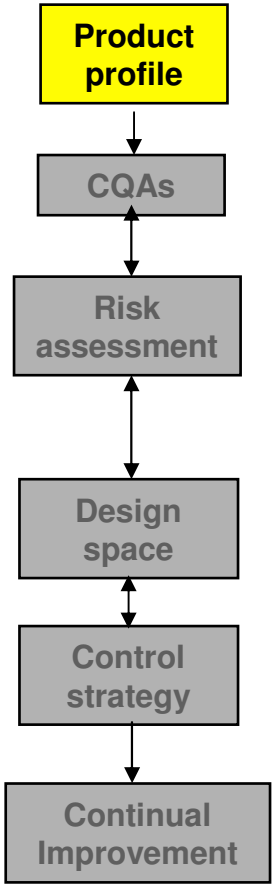
Example QbD Approach - ICH Q8(R2)



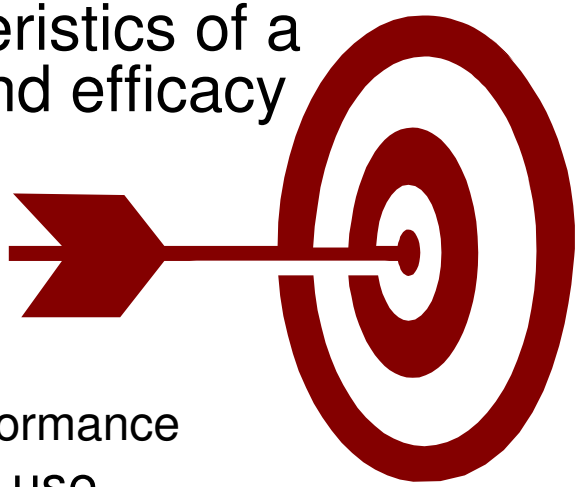
- Target the product profile
- Determine critical quality attributes (CQAs)
- Link raw material attributes and process parameters to CQAs and perform risk assessment
- Develop a design space
- Design and implement a control strategy
- Manage product lifecycle, including continual improvement

Quality Target Product Profile

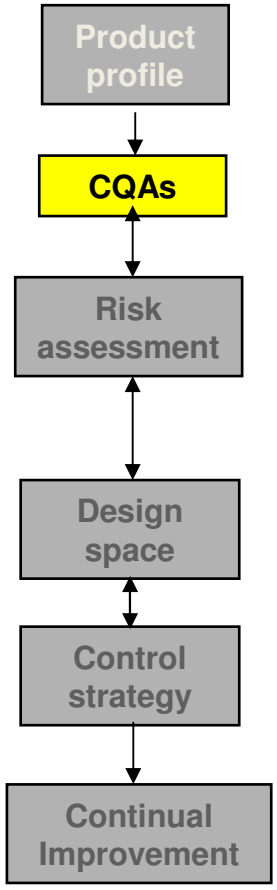
"Begin with the end in mind"



- 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
  - Patient needs – elderly, children
  - Amount of drug per dose
  - Desired dosing schedule
  - Route of administration
  - Safety requirements



Critical Quality Attributes (CQAs)

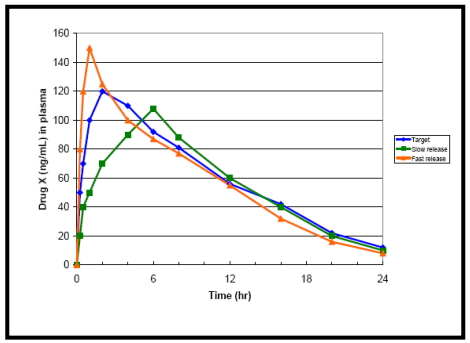


- Physical, chemical, biological or microbiological property or characteristic
- Drug product, drug substance, intermediates, and excipients can possess CQAs
  - Directly affect product quality
  - Affect downstream processability
- Drug product CQAs affect product quality, safety, and/or efficacy
 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

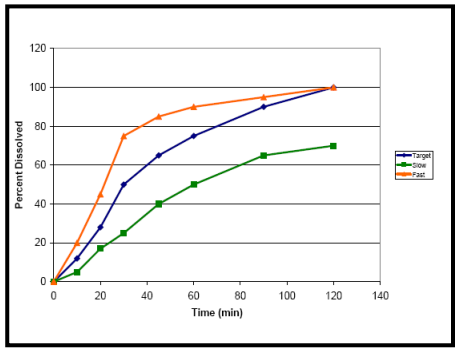
Defining CQAs Example: In Vitro – In Vivo Correlations

Formulation and Manufacturing Process

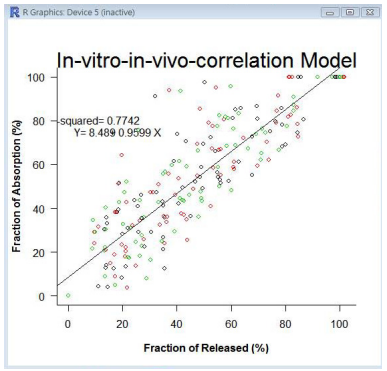
In Vivo Response
(Plasma Conc. Profile)



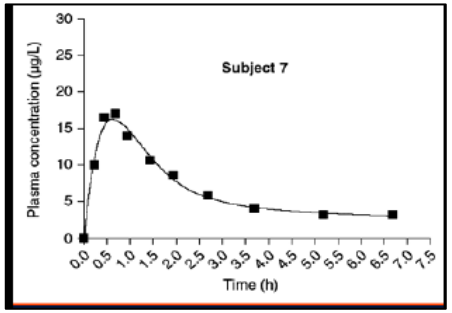
In Vitro Release
(Dissolution Profile)



In Vitro/In Vivo Correlation

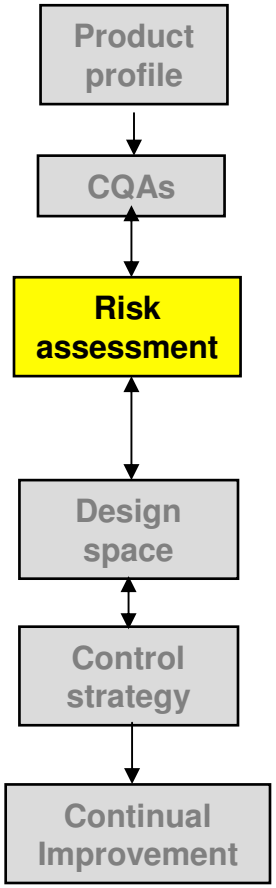


Predictive Model



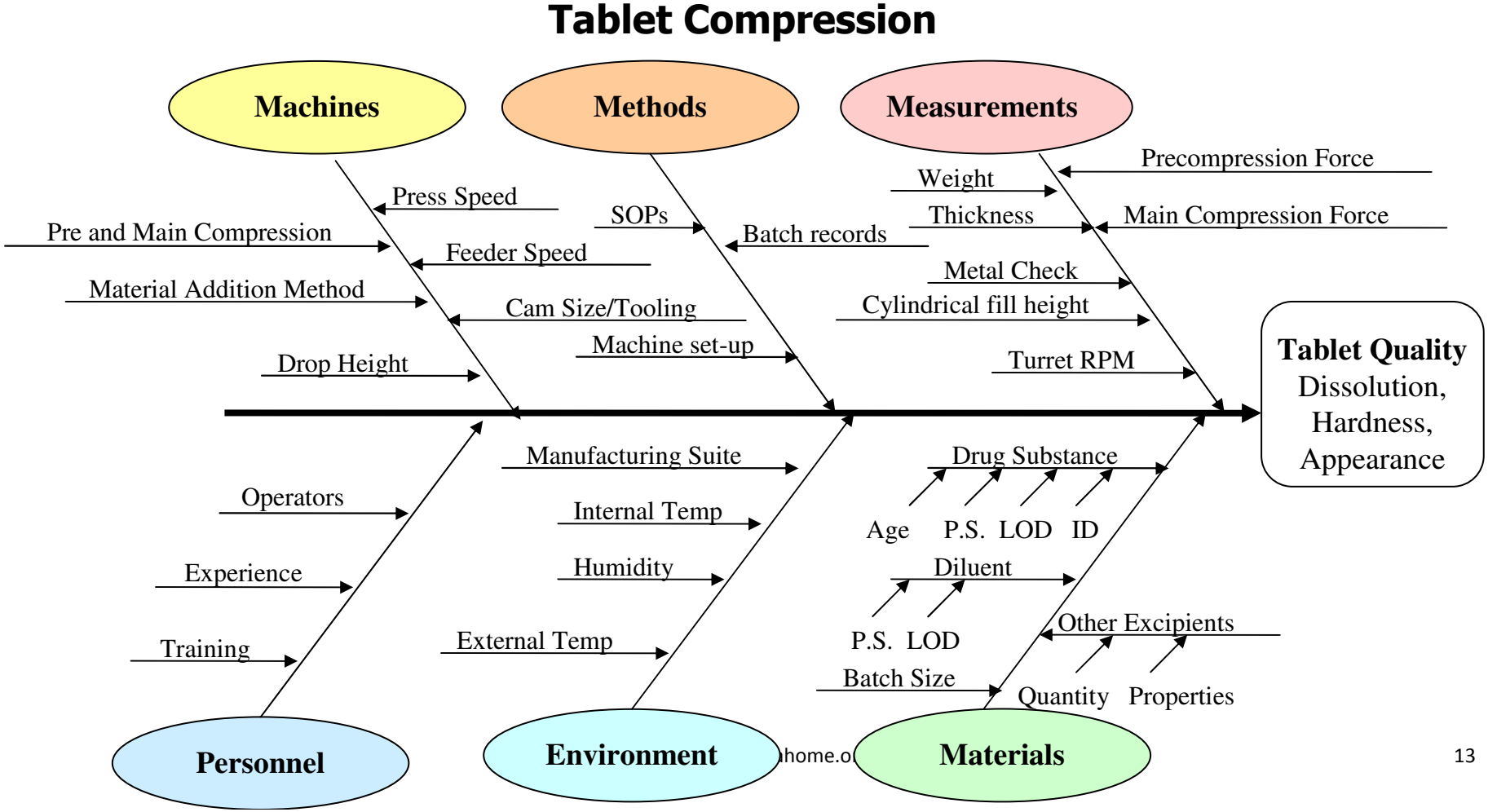
Reference: Medscape, 2002

Risk Management



- A systematic process for the assessment, control, communication and review of risks to the quality of the drug product
- Evaluation of risk to quality should:
  - be based on scientific knowledge
  - link to the protection of the patient
  - Extend over the lifecycle of the product
- Typically conducted with an integrated group of experts, including development and manufacturing

Risk Assessment Example #1
Ishikawa Diagram

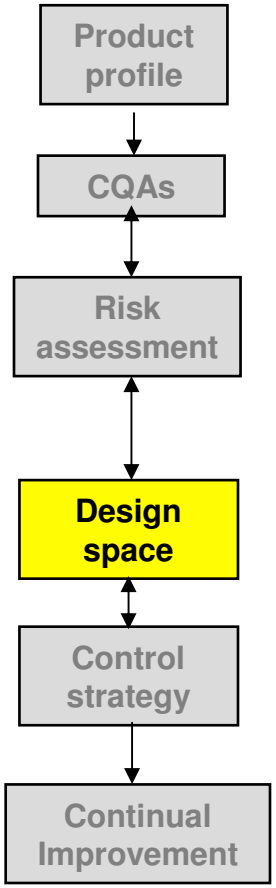


Risk Assessment Example #2
Failure Mode and Effects Analysis

Moisture Sensitive Crystalline Product

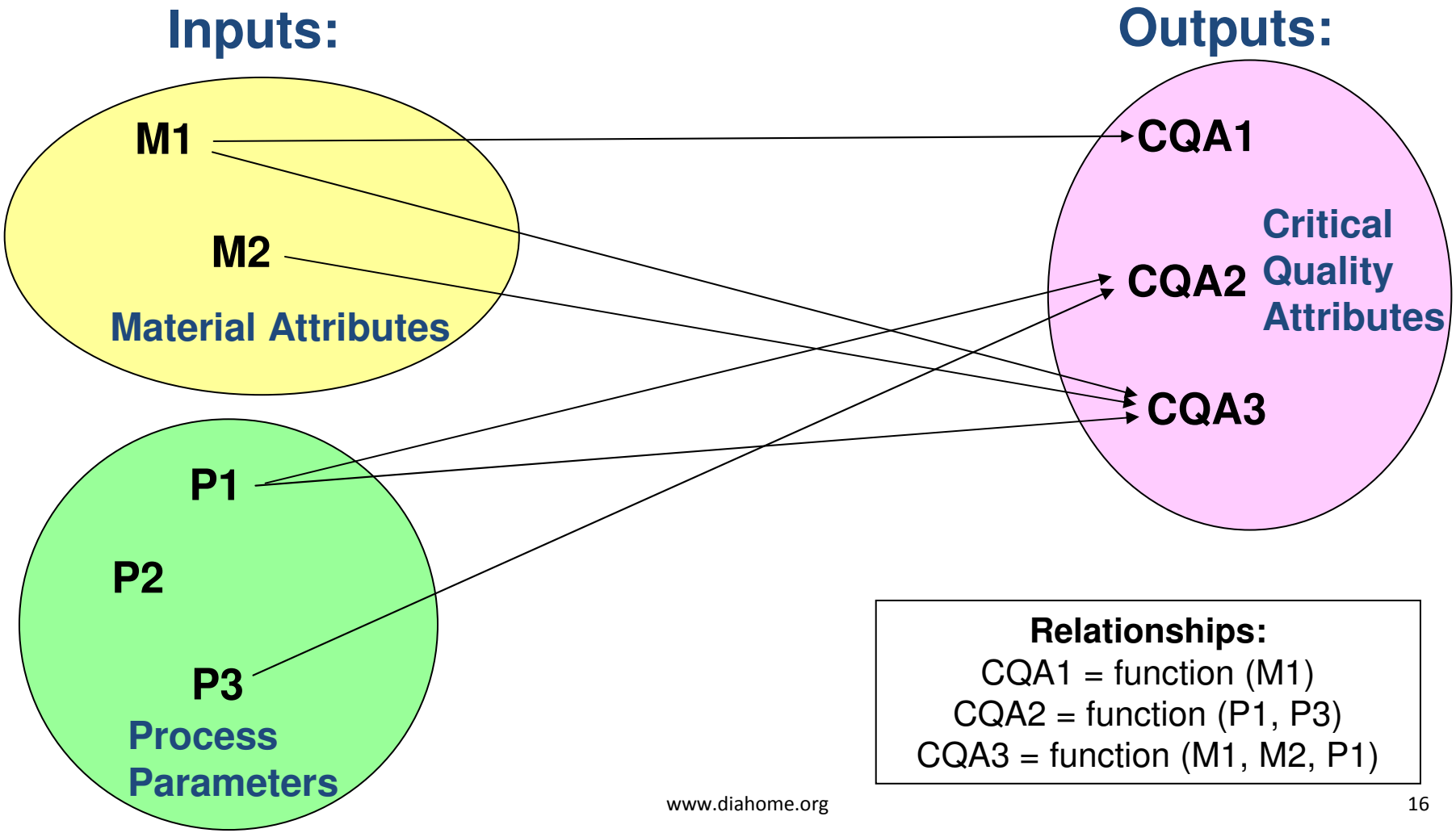
Category	**Process Parameter**	Severity S (1-5)	Occurrence O (1-5)	Detection D (1-5)	Risk priority number S*O*D	Criticality rank
Crystalliztn	Residual solvent	5	4	3	60	1
	Induction time	4	3	2	24	6
	Anti-solvent addition time	5	3	2	30	4
	Mixing	2	2	1	4	11
Isolation/ drying	Temperature during crystal drying	4	4	2	32	3
	Solids transfers	3	1	1	1	13
	Washing effectiveness	2	1	1	2	15
Handling/ storage	Relative humidity	5	3	3	45	2
	Inerting	4	2	3	24	6

Design Space



- 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

Mapping the Linkage



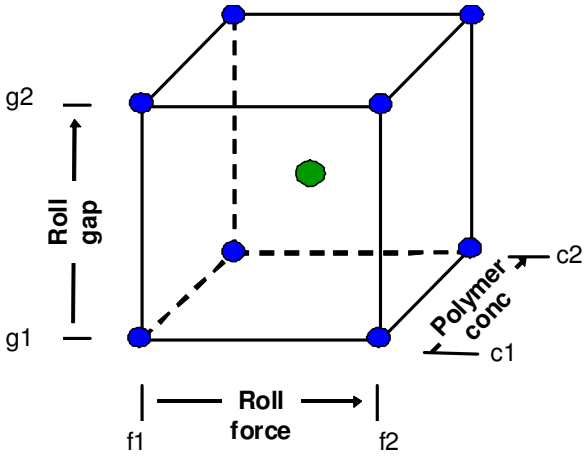
Relationships:
CQA1 = function (M1)
CQA2 = function (P1, P3)
CQA3 = function (M1, M2, P1)

Design Space Determination

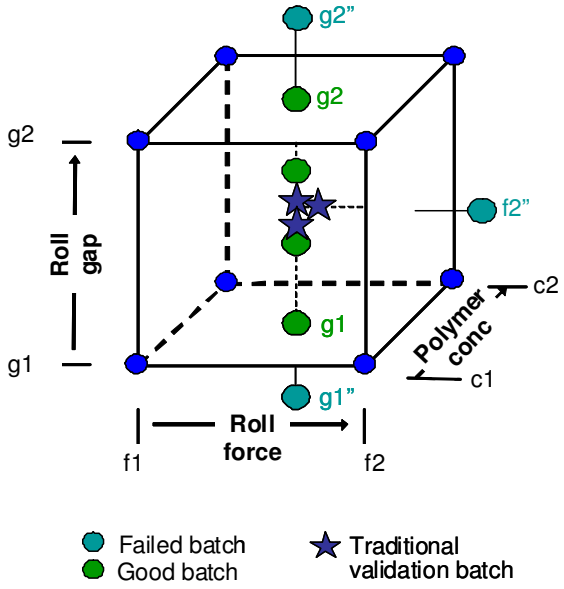
- First-principles approach
  - combination of experimental data and mechanistic knowledge of chemistry, physics, and engineering to model and predict performance
- Non-mechanistic/empirical approach
  - Statistically designed experiments (DOEs)
  - Linear and multiple-linear regression
- Scale-up correlations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

Example - Establishing Design Space

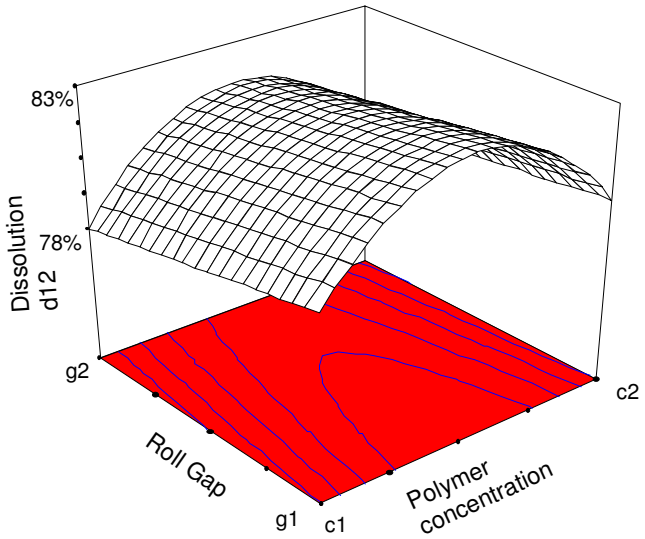
Pilot Scale DOE



Commercial Scale Confirmatory Experiments



Dissolution Response (Design Space)



Input Variables: Polymer concentration, Roll gap, Roll force

Responses: Porosity, Compressibility, Dissolution, Hardness

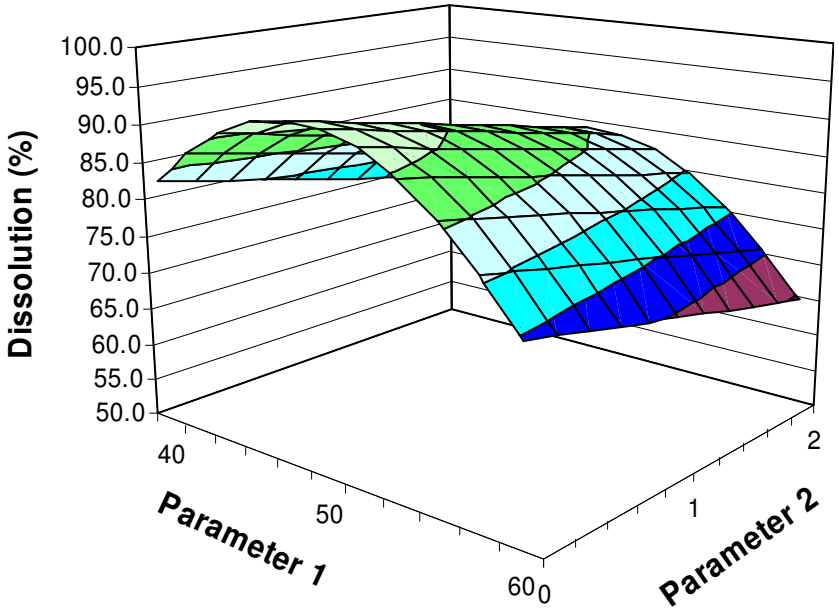
Describing Design Spaces

- 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

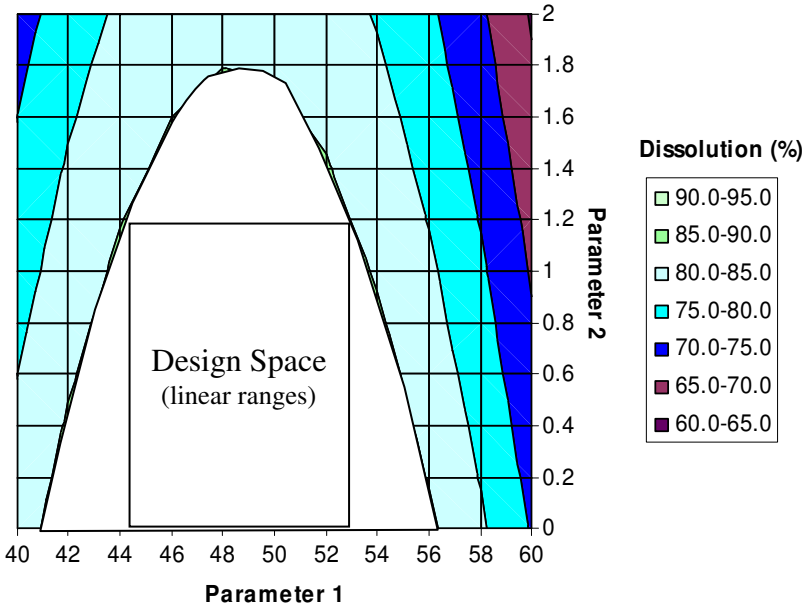
The applicant decides how to describe and present the design space

Example – Describing Design Spaces

Surface Plot

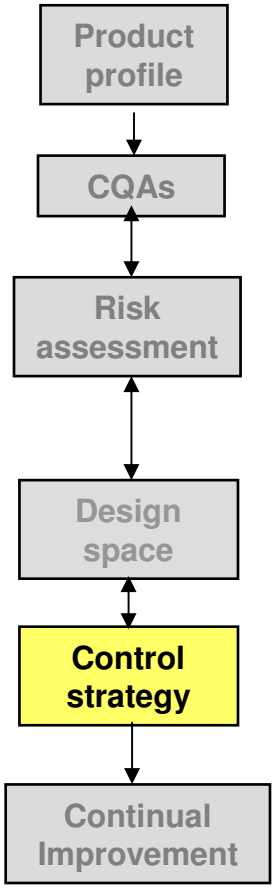


Contour Plot



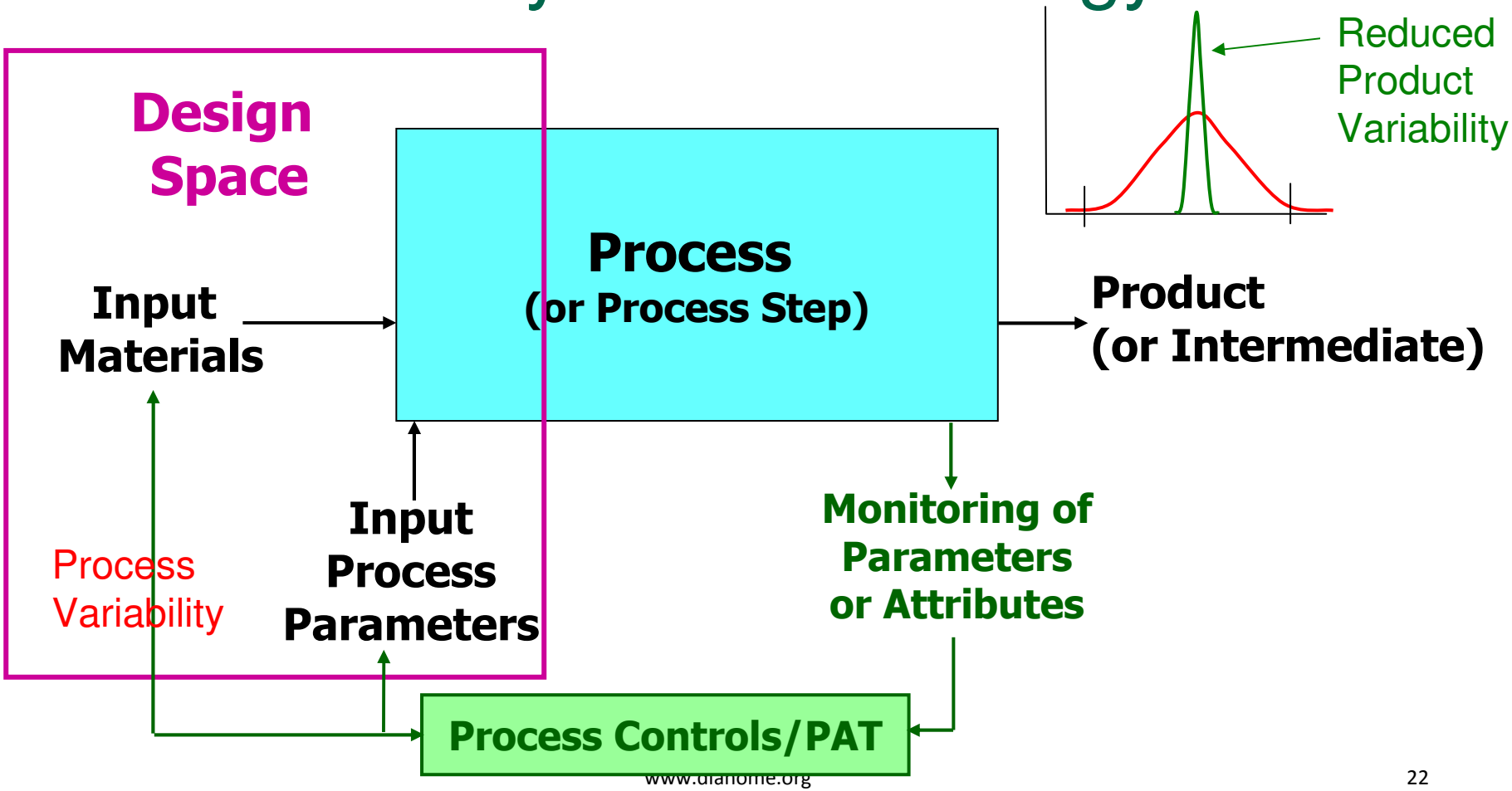
- Design space can be described as a mathematical function or simple parameter range
- Operation within design space will result in a product meeting the defined quality attributes

Control Strategy



- A planned set of controls, derived from current product and process understanding, that assures process performance and product quality (ICH Q10)
- Control strategy can include
  - parameters and attributes related to drug substance and drug product materials and components
  - facility and equipment operating conditions
  - in-process controls
  - finished product specifications
  - associated methods and frequency of monitoring and control

Design Space and Quality Control Strategy

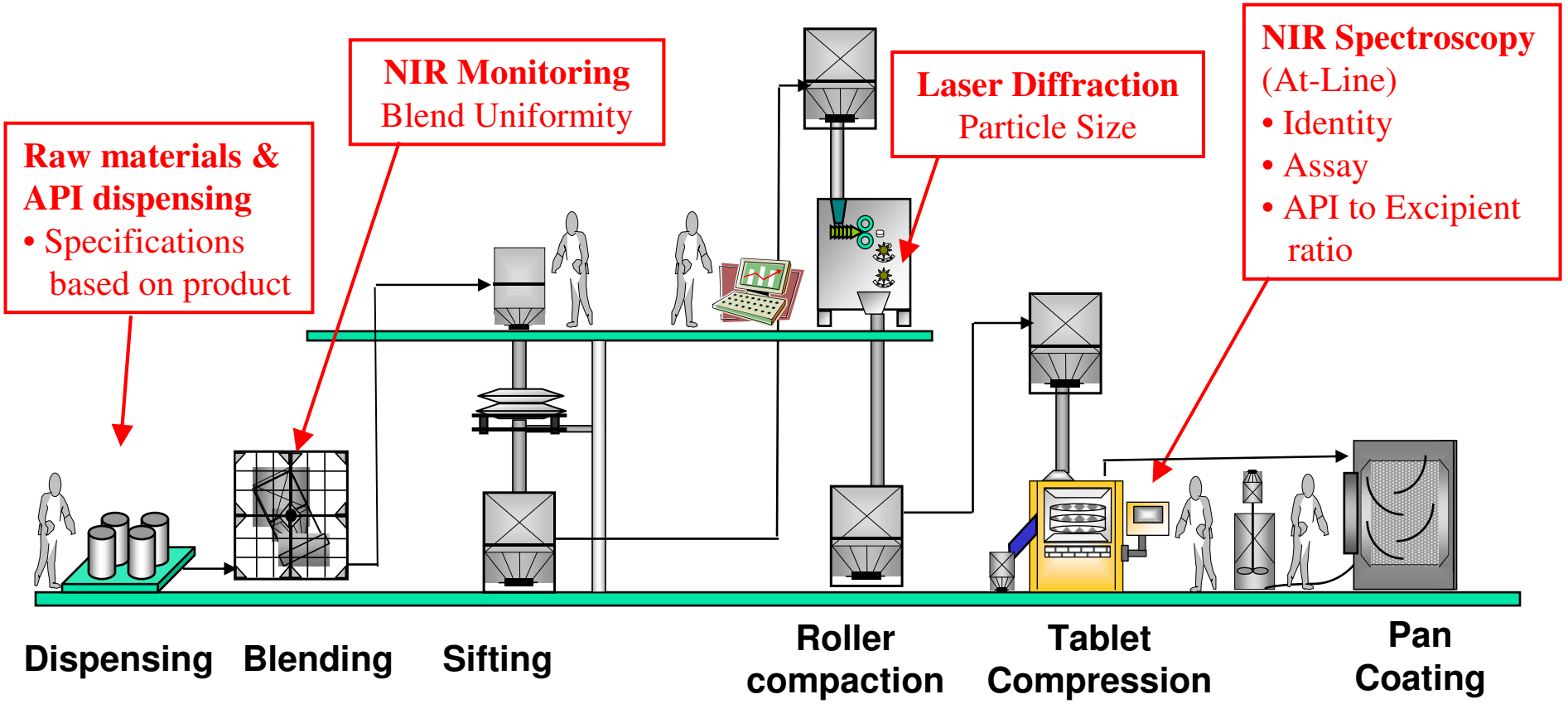


Real Time Release Testing

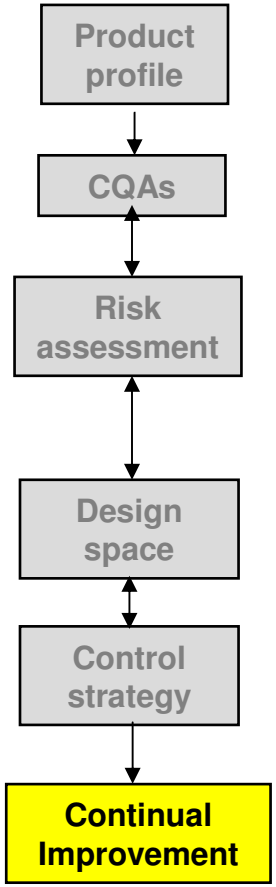
- *The ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically include a valid combination of measured material attributes and process controls* *ICH Q8(R2)*
- Manufacturing flexibility
  - Increased manufacturing efficiency
  - Measure and control in real-time
- Increased assurance of quality
  - Science based release criteria
  - More representative of process

A more modern approach to manufacturing and control

Control Strategy Example – Real Time Release



Continual Improvement



- Lifecycle risk management
  - Use development information as starting point
  - Update as experience gained
- Process tracking and trending
  - Statistical process control
  - Adjust trends before they become problems
- Knowledge management
- Model maintenance and updating

FDA Review Office Programs

- Office of New Drug Quality Assessment (ONDQA)
  - Pharmaceutical Quality Assessment System (PQAS)
  - 2005 CMC Pilot program
- Office of Biotechnology Products
  - 2008 Biotechnology Pilot Program
- Office of Generic Drugs
  - Question Based Review (QBR)
  - Workshops on QbD for generic drugs

ONDQA's CMC Pilot Program

- Objectives
  - To provide participating firms an opportunity to submit CMC information demonstrating QbD
  - To enable FDA to implement new QbD concepts
- Status – complete
  - First announced June 2005
  - 9 original and 2(3) supplemental NDAs accepted
  - 11 approved, 1 withdrawn for non-CMC reasons
- Common factors
  - Submission of design space
  - Use of risk assessment
  - Proposals of regulatory flexibility under firm's quality system

CMC Pilot Observations

- Wide variety of design spaces proposed:
  - Most included drug product, some included drug substance
  - Most included process parameters, some included formulation components
  - Developed using varied experimental techniques & mathematical models
  - Several utilized risk assessment in development
- Wide variety of control strategies utilized, including
  - On-line analyzers
  - In-process testing in lieu of end-product tests
  - Real time release testing using PAT

Findings from CMC 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
- Learning has been incorporated into ICH Q8R
- Refinement of concepts still ongoing
  - QbD applications within and outside of pilot program

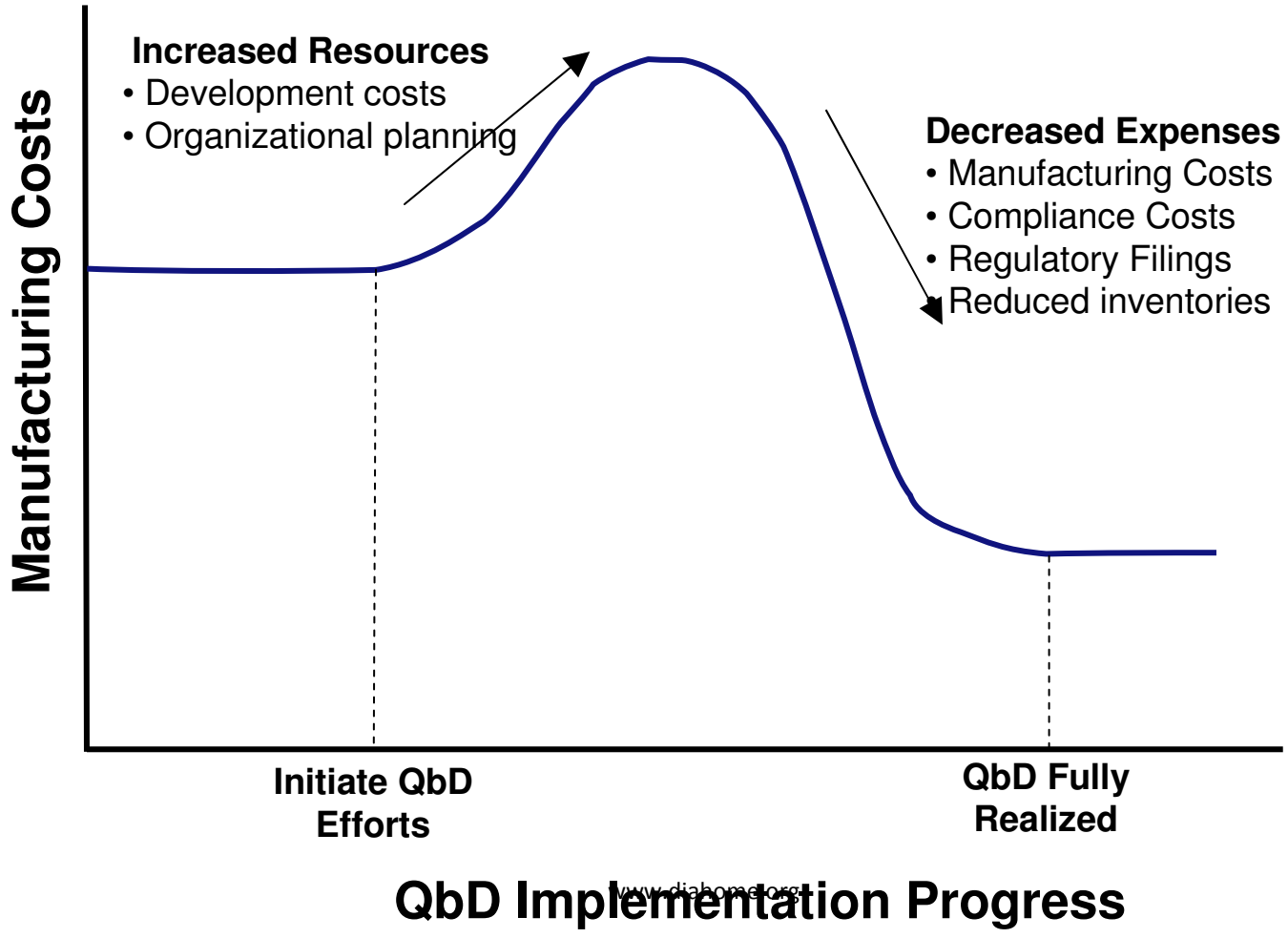
Recent QbD Experiences- Outside the CMC Pilot

- Number of QbD meetings and applications have been increasing
- Number of submissions containing QbD elements received in 2008 & 2009 outside of pilot
  - 12 NDAs
  - 6 supplemental NDAs
- New proposals have contained challenging regulatory approaches
- Additional experience is helping to coalesce review approaches

Challenges for QbD

- Culture challenges
  - Move from prescriptive approach
  - More sharing of scientific and risk information
- Business Challenges
  - Business justification
  - Management Support
  - Budgeting silos across business units
- Implementation Challenges
  - Collaboration between functions
  - Experience with new concepts
  - Workload and resource limitations
- International harmonization

Potential Costs & Benefits of QbD



Concluding Thoughts

- FDA and ICH quality initiatives are enabling a fundamental paradigm shift in pharmaceutical manufacturing:
  - Quality control strategies based on product knowledge and process understanding
  - A more scientific and risk-based regulatory oversight
- 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

Thank you!

Questions, comments, concerns:

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